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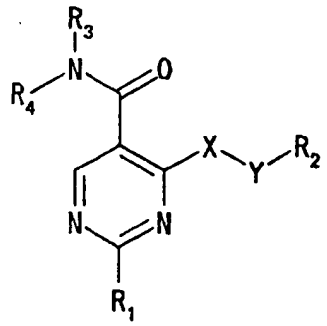
(54) PYRIMIDINE-5-CARBOXAMIDE COMPOUNDS, PROCESS FOR PRODUCING THE SAME AND USE THEREOF

(57) A compound of the formula



wherein R_1 is a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 nitrogen atom(s), which heterocycle is attached by a secondary nitrogen atom constituting the heterocycle; X is an oxygen atom, a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom(s) or a sulfur atom optionally oxidized with 1 or 2 oxygen, Y is a bond or a C_{1-5} alkylene group, R_2 is (1) a hydrogen atom, (2) a hydroxy group, (3) a C_{1-5} alkoxy group, (4) a C_{1-5} alkylthio group, (5) a carbocycle having 3 to 15 carbon atoms or (6) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s), provided that when Y is a bond, R_2 is a carbocycle having 3 to 15 carbon atoms or a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and; one

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of R_3 and R_4 is a hydrogen atom or a group of the formula: -Z-R_5 (Z is a bond or C_{1-10} alkylene group optionally having substituent(s) and R_5 is (1) a hydrogen atom, (2) a hydroxy group, (3) a C_{1-5} alkoxy group, (4) a nitrile group, (5) a C_{1-5} alkoxy-carbonyl group, (6) a carboxyl group, (7) a carbamoyl group, (8) a (mono or di-C_{1-5} alkyl)carbamoyl group, (9) an amino group, (10) a (di or mono-C_{1-5} alkyl)amino group, (11) a (C_{1-5} alkoxy-carbonyl)amino group, (12) a C_{1-5} alkylthio group, (13) a carbocycle having 3 to 15 carbon atoms or (14) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s)); the other is a group of the formula: -Z-R_5 (Z and R_5 are as defined above); and R_3 and R_4 may form, together with the adjacent nitrogen atom, a heterocycle having a skeleton consisting of 3 to 15 atoms, which heterocycle is attached by a secondary nitrogen atom constituting the heterocycle, wherein the above-mentioned heterocycle and a carbocycle having 3 to 15 carbon atoms are each optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl, or a salt thereof or a prodrug thereof have a superior cGMP specific phosphodiesterase (PDE) inhibitory activity, and can be used as an agent for the prophylaxis or treatment of cardiovascular diseases such as angina pectoris, heart failure, cardiac infarction, hypertension, arteriosclerosis and the like, allergic diseases such as asthma, or disorders of male or female genital function and the like.

Description

Technical field

[0001] The present invention relates to a novel pyrimidine-5-carboxamide compound or a salt thereof, a production method and a pharmaceutical product containing the same. The pyrimidine-5-carboxamide compound and a salt thereof of the present invention have a potent and selective cyclic guanosine-3',5'-monophosphoric acid (hereinafter cGMP) phosphodiesterase (hereinafter PDE) inhibitory activity, and are useful as an agent for the prophylaxis or therapy of a disease for which its action is effective.

Background Art

[0002] cGMP is biosynthesized from guanosine triphosphate (GTP) by the action of guanylate cyclase and metabolized to 5'-GMP by the action of cGMP-PDE, during which cGMP plays various roles as a secondary transmitter in cellular signal transduction in the body. Particularly the action of cGMP, which is of critical importance in the functional modulation of cardiovascular system, is well known. Therefore, inhibition of the action of cGMP-PDE leads to the prophylaxis or treatment of the diseases caused by the promotion of metabolism of cGMP. Examples of such diseases include angina pectoris, heart failure, cardiac infarction, hypertension, pulmonary hypertension, arteriosclerosis, allergic diseases, asthma, renal diseases, cerebral function disorders, immunodeficiency, ophthalmic diseases, disorders of male or female genital function and the like.

[0003] There are a number of reports on a compound having a PDE inhibitory activity (e.g., WO9853819 and references cited therein). However, only a small number of reports deal with a compound having a monocyclic pyrimidine skeleton and showing a PDE inhibitory activity, which are limited to JP-A-2-295978, JP-A-3-145466, JP-A-7-89958, Korean J. of Med. Chem., vol. 8, p. 6 (1998) and the like.

[0004] PDE is known to include at least 7 isoenzymes [e.g., Annual Reports in Medicinal Chemistry, vol. 31, p. 61 (1996), Academic Press, San Diego]. Of those isoenzymes, PDE I, II, III, IV and V are widely distributed in the body. It is well known that inhibition of plural isoenzymes results in unpreferable occurrence of side effects.

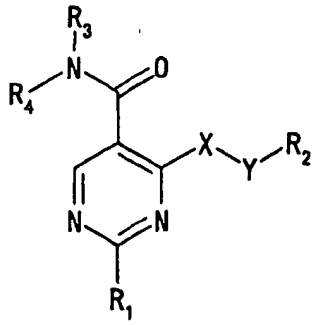
[0005] It is therefore an object of the present invention to provide a potent and selective PDE inhibitor.

Disclosure Of Invention

[0006] For the purpose of achieving the above-mentioned object, the present inventors have synthesized various compounds and succeeded in creating a compound having a novel structure represented by the formula (I) and found that the compound has a potent and selective PDE inhibitory activity, which resulted in the completion of the present invention.

[0007] Accordingly, the present invention provides

[1] a compound of the formula



(I)

wherein

R_1 is a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 nitrogen atom(s), which heterocycle is attached by a secondary nitrogen atom constituting the heterocycle;

X is an oxygen atom, a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom

(s) or a sulfur atom optionally oxidized with 1 or 2 oxygen,

Y is a bond or a C_{1-5} alkylene group,

R_2 is (1) a hydrogen atom, (2) a hydroxy group, (3) a C_{1-5} alkoxy group, (4) a C_{1-5} alkylthio group, (5) a carbocycle having 3 to 15 carbon atoms or (6) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s),

provided that when Y is a bond, R_2 is a carbocycle having 3 to 15 carbon atoms or a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and;

one of R_3 and R_4 is a hydrogen atom or a group of the formula: -Z-R_5 (Z is a bond or C_{1-10} alkylene group optionally having substituent(s) and R_5 is (1) a hydrogen atom, (2) a hydroxy group, (3) a C_{1-5} alkoxy group, (4) a nitrile group, (5) a C_{1-5} alkoxy-carbonyl group, (6) a carboxyl group, (7) a carbamoyl group, (8) a (mono or di-C_{1-5} alkyl)carbamoyl group, (9) an amino group, (10) a (di or mono-C_{1-5} alkyl)amino group, (11) a (C_{1-5} alkoxy-carbonyl)amino group, (12) a C_{1-5} alkylthio group, (13) a carbocycle having 3 to 15 carbon atoms or (14) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s));

the other R_3 and R_4 is a group of the formula: -Z-R_5 (Z and R_5 are as defined above); and may form, together with the adjacent nitrogen atom, a heterocycle having a skeleton consisting of 3 to 15 atoms, which heterocycle is attached by a secondary nitrogen atom constituting the heterocycle, wherein the above-mentioned heterocycle and a carbocycle having 3 to 15 carbon atoms are each optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl) amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl,

or a salt thereof,

[2] the compound of [1], wherein, when Z is a C_{2-10} alkylene group optionally having substituent(s), R_5 is a hydrogen atom, a hydroxy group, a C_{1-5} alkoxy group, a nitrile group, a C_{1-5} alkoxy-carbonyl, a carboxyl group, a carbamoyl group, a (mono or di-C_{1-5} alkyl)carbamoyl group, an amino group, a (di or mono-C_{1-5} alkyl)amino group, a (C_{1-5} alkoxy-carbonyl)amino group, a C_{1-5} alkylthio group, a carbocycle having 3 to 15 carbon atoms, or a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and, when Z is a methylene group optionally having substituents, R_5 is a nitrile group, a C_{1-5} alkoxy-carbonyl group, a carboxyl group, a carbamoyl group, a (mono or di-C_{1-5} alkyl)carbamoyl group, a carbocycle having 3 to 15 carbon atoms, or a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and,

[3] the compound of [1], wherein X is a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom(s) or a sulfur atom optionally oxidized with 1 or 2 oxygen,

[4] the compound of [1], wherein Y is a C_{2-5} alkylene group,

[5] the compound of [1], wherein Y is a C_{1-5} alkylene group, R_2 is a hydroxy group, a C_{1-5} alkoxy group or a C_{1-5} alkylthio group,

[6] the compound of [1], wherein R_5 is (1) a non-aromatic carbocycle having 3 to 15 carbon atoms or (2) a non-aromatic heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s),

[7] the compound of [1], wherein Z is a C_{2-10} alkylene group optionally having substituent(s), and R_5 is a hydroxy group, a nitrile group, a C_{1-5} alkoxy-carbonyl, a carboxyl group, a carbamoyl group, a (mono or di-C_{1-5} alkyl) carbamoyl group, a (C_{1-5} alkoxy-carbonyl)amino group or a C_{1-5} alkylthio group,

[8] the compound of [1], wherein Z is a methylene group optionally having substituent(s), and R_5 is a nitrile group, a C_{1-5} alkoxy-carbonyl group, a carboxyl group, a carbamoyl group or a (mono or di-C_{1-5} alkyl)carbamoyl group,

[9] the compound of [1], wherein the substituent(s) of the heterocycle and the carbocycle having 3 to 15 carbon atoms is selected from the group consisting of C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-3} alkylenedioxy, hydroxy, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl,

[10] the compound of [1], wherein R_1 is a heterocycle having a skeleton consisting of 5 to 12 atoms including 1 or 2 nitrogen atom(s) and optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl)(C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thi-

oxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl) sulfamoyl,

[11] the compound of [1], wherein R_1 is a heterocycle having a skeleton consisting of 8 to 12 atoms including a nitrogen atom and optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl)(C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl,

[12] the compound of [1], wherein R_1 is 1-indolinyl optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl) amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl,

[13] the compound of [1], wherein R_2 is a carbocycle having 5 to 7 carbon atoms or a heterocycle having a skeleton consisting of 5 to 7 atoms including 1 or 2 heteroatom(s), which heterocycle is optionally substituted by substituent (s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl) amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl) sulfamoyl,

[14] the compound of [1], wherein R_2 is phenyl optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl) amino, (C_{1-5} alkoxy-carbonyl) amino, (C_{1-5} acyl) amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl,

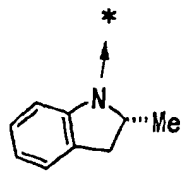
[15] the compound of [1], wherein X is an oxygen atom or NH, and Y is a C_{1-3} alkylene group,

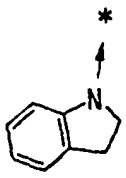
[16] the compound of [1], wherein X is an oxygen atom, and Y is a methylene group,

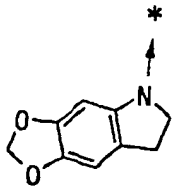
[17] the compound of [1], wherein R_3 is a hydrogen atom and R_4 is a group of the formula: -Z-R_5,

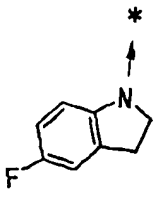
[18] the compound of [17], wherein Z is a bond or a C_{1-4} alkylene group, R_5 is a carbocycle having 5 to 8 carbon atoms or a heterocycle having a skeleton consisting of 5 to 11 atoms having 1 to 5 heteroatom(s), which heterocycle is optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl,

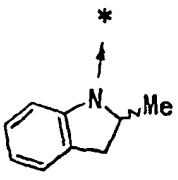
[19] the compound of [1], wherein R_1 is a group selected from

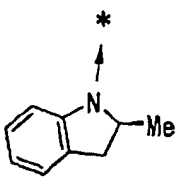


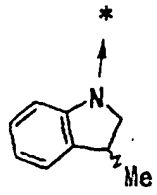


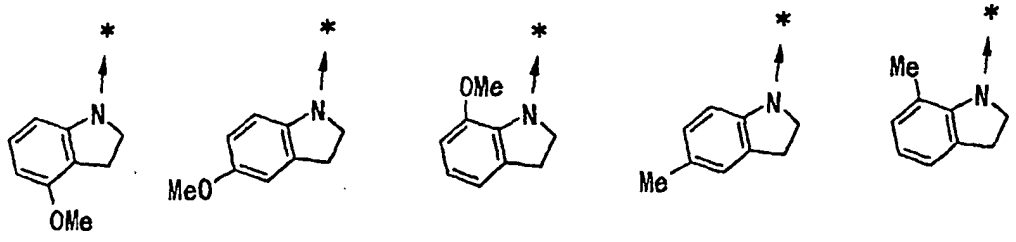


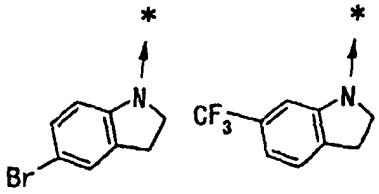




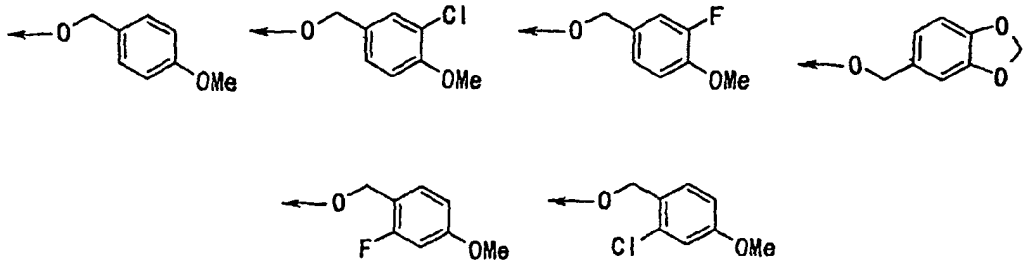


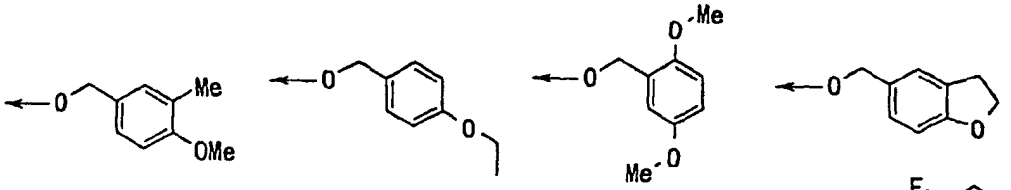


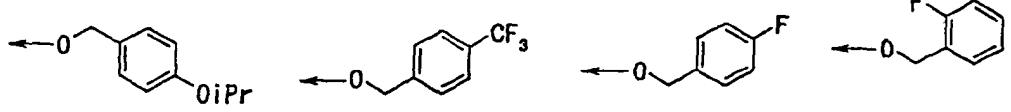


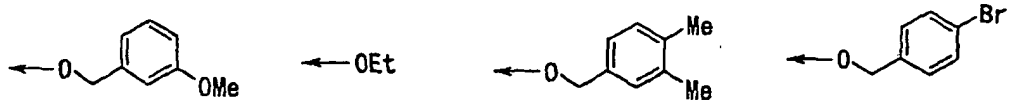


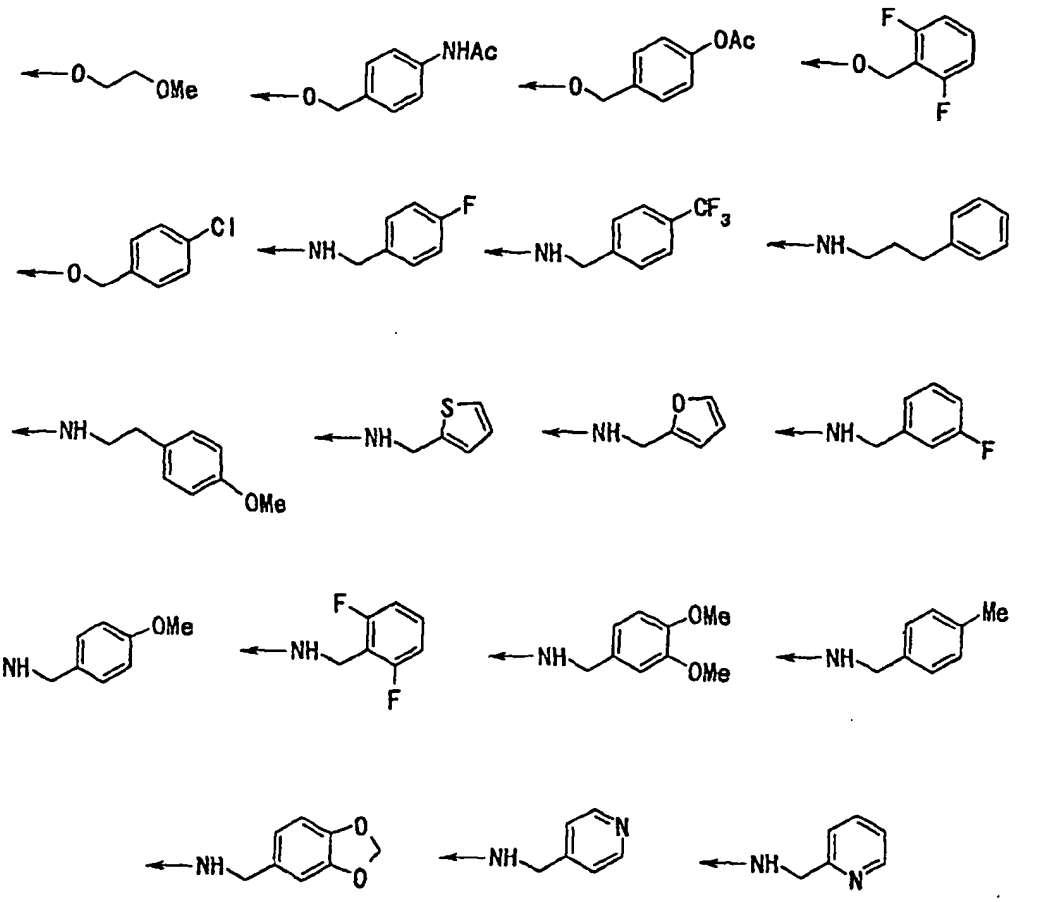
, -X-Y-R_2 is a group selected from



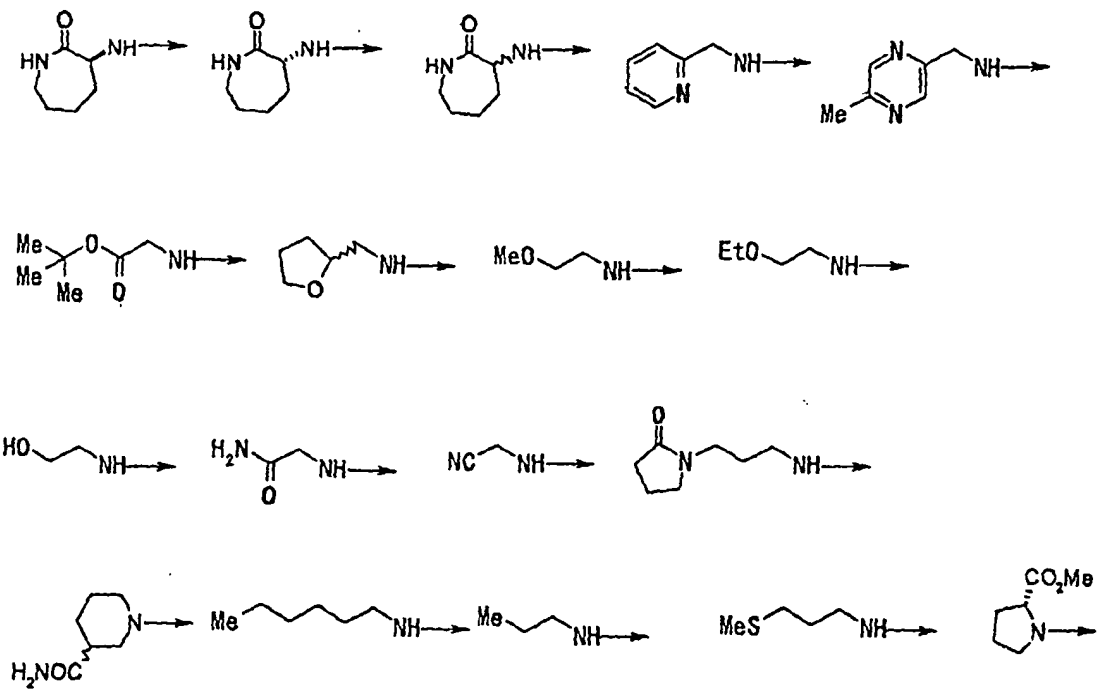


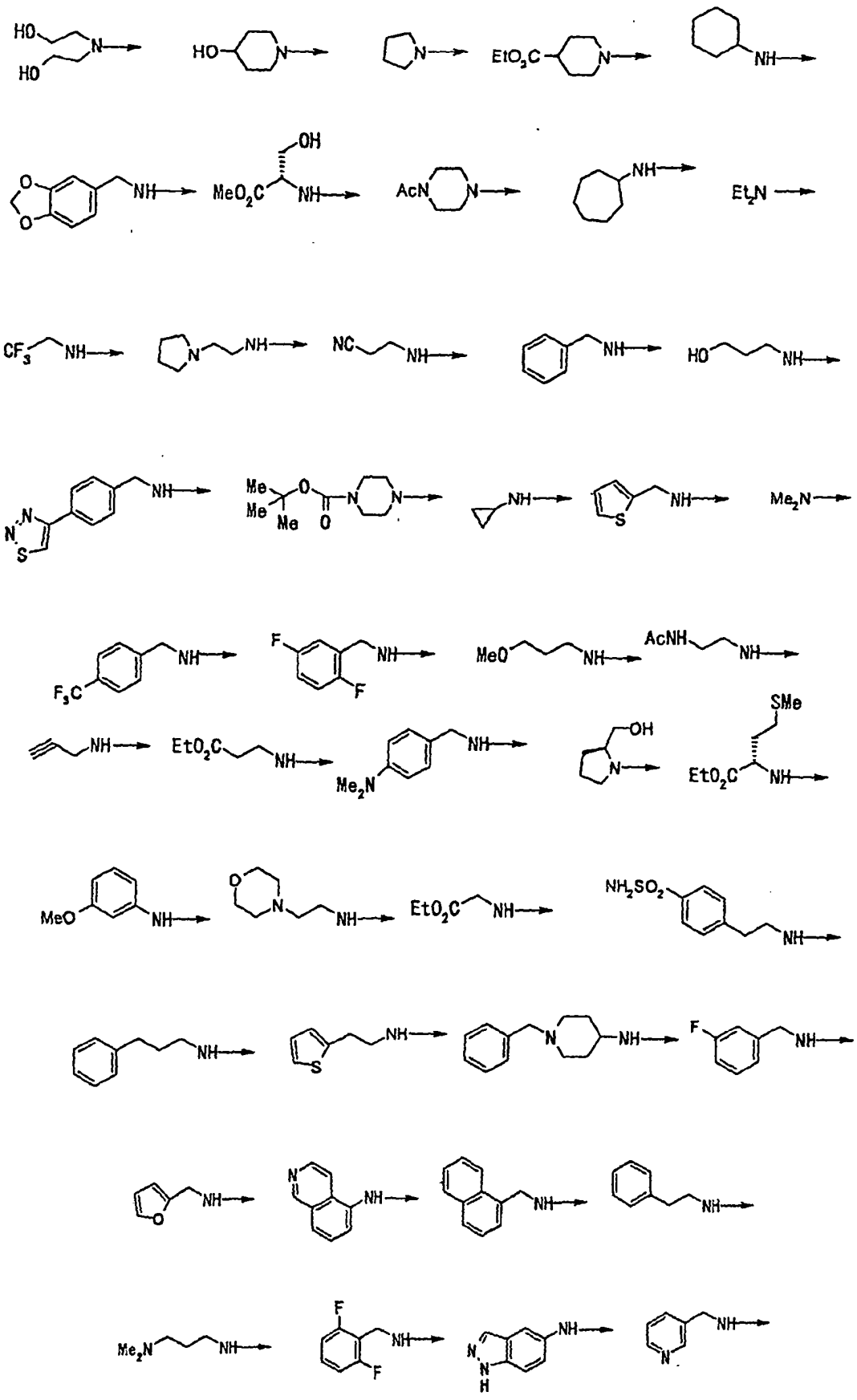


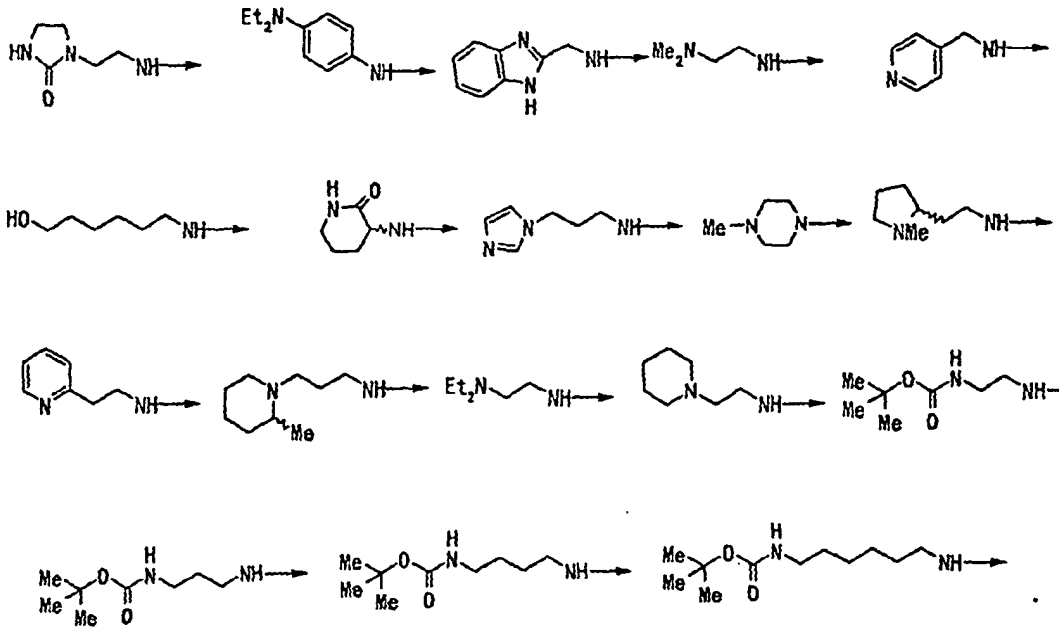




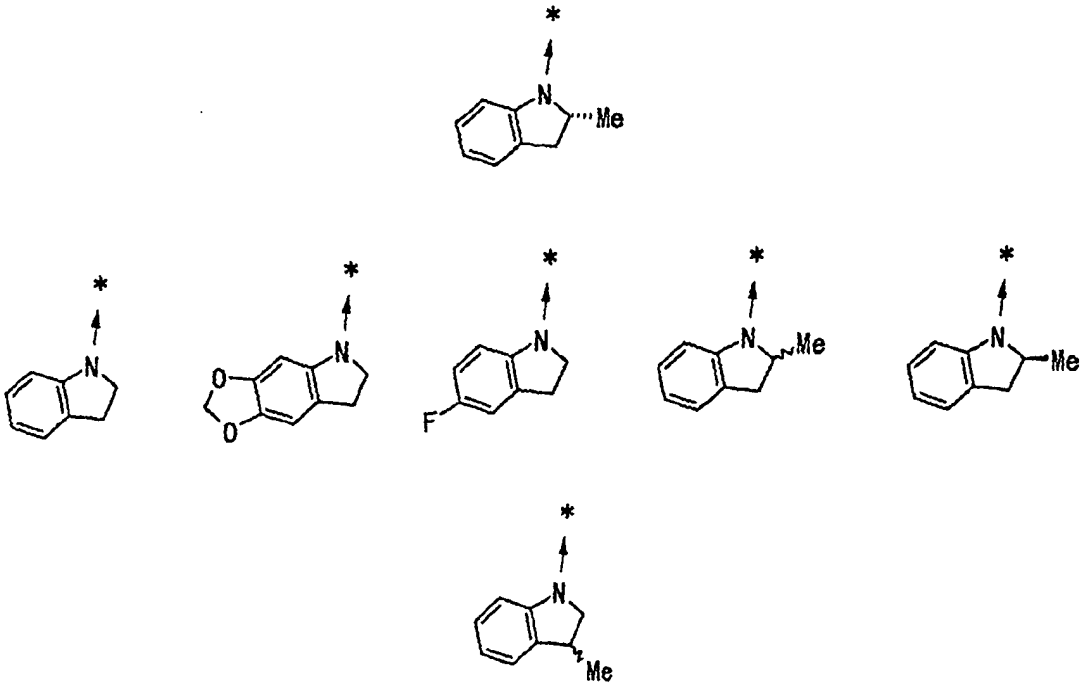
, and -NR_3R_4 is a group selected from



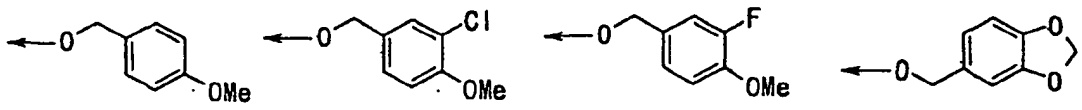


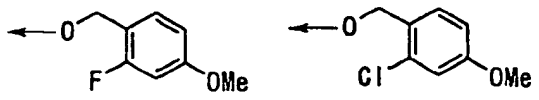


[20] the compound of [1], wherein R_1 is a group selected from

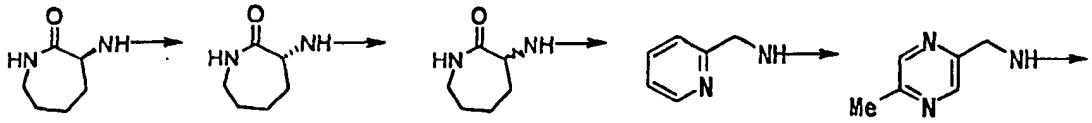


, -X-Y-R_2 is a group selected from

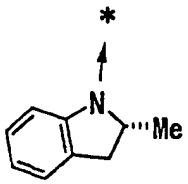




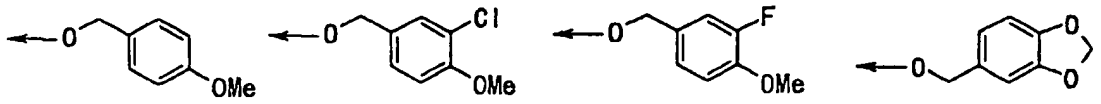
, and $-NR_3R_4$ is a group selected from



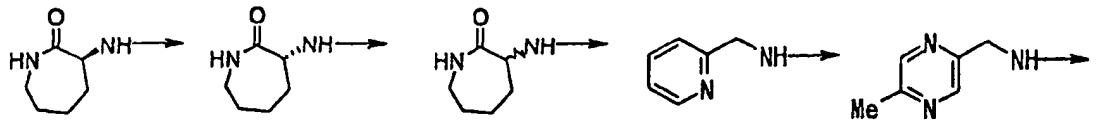
[21] the compound of [1], wherein R_1 is a group selected from the group consisting of



, $-X-Y-R_2$ is a group selected from the group consisting of



, and $-NR_3R_4$ is a group selected from the group consisting of

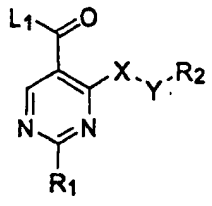


[22] (i) (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide, (ii) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide, (iii) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide, (iv) (RS)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide, (v) 4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide, (vi) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide, (vii) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide, (viii) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide, (ix) 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide, (x) 4-[(3-chloro-4-methoxybenzyl)oxy]-

2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide, (xi) 4-[(3-chloro-4-methoxybenzyl) oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide, (xii) (rac)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide, (xiii) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xiv) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xv) 4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xvi) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy] -N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xvii) 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xviii) 4-[(4-methoxybenzyl)oxy]-2-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xix) 4-[(4-methoxybenzyl)oxy]-2-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xx) 4-[(4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xxi) 4-[(4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xxii) 2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xxiii) 4-[(3-chloro-4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xxiv) 4-[(4-methoxybenzyl)oxy]-2-[(2S)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide or (xxv) 4-[(4-methoxybenzyl)oxy]-2-[(2S)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide,

[23] a prodrug of the compound of [1],

[24] a production method of the compound of [1], which comprises reacting a compound of the formula



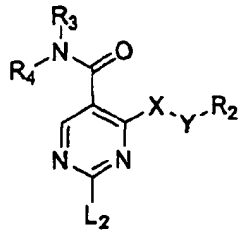
(II)

wherein L_1 is a leaving group and other symbols are as defined in [1], or a salt thereof, with an amine compound of the formula

$$R_3R_4NH$$

wherein R_3 and R_4 are as defined in [1],

[25] a production method of the compound of [1], which comprises reacting a compound of the formula



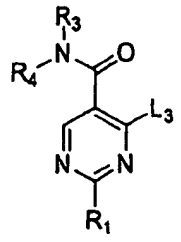
(III)

wherein L_2 is a leaving group and other symbols are as defined in [1], or a salt thereof, with a compound of the formula

$$R_1\text{-}H$$

wherein R_1 is as defined in [1],

[26] a production method of the compound of [1], which comprises reacting a compound of the formula



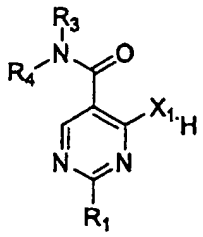
(IV)

wherein L_3 is a leaving group and other symbols are as defined in [1], or a salt thereof, with a compound of the formula

$$R_2\text{-}Y\text{-}X_1\text{-}H$$

wherein R_2 and Y are as defined in [1] and X_1 is an oxygen atom, a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom(s) or a sulfur atom, and if desired, subjecting the resulting compound to oxidation,

[27] a production method of the compound of [1], which comprises reacting a compound of the formula



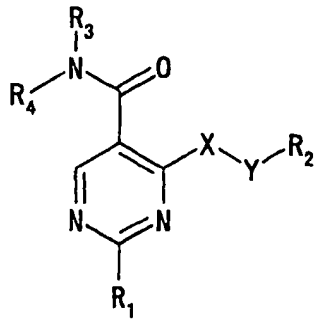
(V)

wherein symbols are as defined in [1], X_1 is an oxygen atom, a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom(s) or a sulfur atom, or a salt thereof, with a compound of the formula

$$R_2\text{-}Y\text{-}L_4$$

wherein R_2 and Y are as defined in [1] and L_4 is a leaving group, and if desired, subjecting the resulting compound to oxidation,

[28] a pharmaceutical composition comprising a compound of the formula



(I)

wherein symbols are as defined in [1], or a salt thereof or a prodrug thereof,

[29] the pharmaceutical composition of [28], which is a cyclic guanosine-3',5'-monophosphoric acid phosphodiesterase (particularly, cyclic guanosine-3',5'-monophosphoric acid phosphodiesterase V) inhibitor,

[30] the pharmaceutical composition of [28], which is a composition for the prophylaxis or treatment of angina pectoris, heart failure, cardiac infarction, hypertension, pulmonary hypertension, arteriosclerosis, allergic diseases, asthma, renal diseases, cerebral function disorders, immunodeficiency, ophthalmic diseases or disorders of male or female genital function,

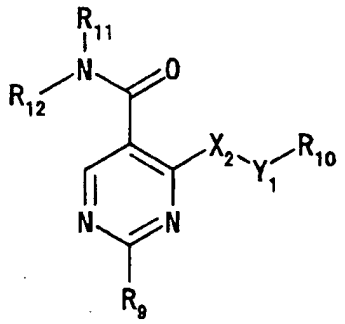
[31] a method for inhibiting cyclic guanosine-3',5'-monophosphoric acid phosphodiesterase, which comprises administering an effective amount of the compound of [1] or a prodrug thereof to a mammal,

[32] a method for the prophylaxis or treatment of angina pectoris, heart failure, cardiac infarction, hypertension, pulmonary hypertension, arteriosclerosis, allergic diseases, asthma, renal diseases, cerebral function disorders, immunodeficiency, ophthalmic diseases or disorders of male or female genital function in a mammal, which comprises administering an effective amount of the compound of [1] or a prodrug thereof to the mammal,

[33] use of the compound of [1] or a prodrug thereof for the production of a cyclic guanosine-3',5'-monophosphoric acid phosphodiesterase inhibitor,

[34] use of the compound of [1] or a prodrug thereof for the production of an agent for the prophylaxis or treatment of angina pectoris, heart failure, cardiac infarction, hypertension, pulmonary hypertension, arteriosclerosis, allergic diseases, asthma, renal diseases, cerebral function disorders, immunodeficiency, ophthalmic diseases or disorders of male or female genital function,

[35] a compound of the formula



(I')

wherein

R_9 is a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 nitrogen atom(s), and optionally having substituent(s), which heterocycle is attached by a secondary nitrogen atom forming the heterocycle,

X_2 is an oxygen atom, a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom(s) or a sulfur atom optionally oxidized with 1 or 2 oxygen,

Y_1 is a bond or a C_{1-5} alkylene group,

R_{10} is (1) a hydrogen atom, (2) a hydroxy group, (3) a C_{1-5} alkoxy group, (4) a C_{1-5} alkylthio group, (5) a C_{3-15} carbocycle optionally having substituent(s) or (6) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and optionally having substituent(s), one of R_{11} and R_{12} is a hydrogen atom or a group of the formula: $-Z_1-R_{13}$ (Z_1 is a bond or a C_{1-10} alkylene group optionally having substituent(s)), R_{13} is (1) a hydrogen atom, (2) a hydroxy group, (3) a C_{1-5} alkoxy group, (4) a nitrile group, (5) a C_{1-5} alkoxy-carbonyl group, (6) a carboxyl group, (7) a carbamoyl group, (8) a (mono or di-C_{1-5} alkyl)carbamoyl group, (9) an amino group, (10) a (di or mono-C_{1-5} alkyl)amino group, (11) a (C_{1-5} alkoxy-carbonyl)amino group, (12) a C_{1-5} alkylthio group, (13) a C_{3-15} carbocycle optionally having substituent(s) or (14) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and optionally having substituent(s),

the other R_{11} and R_{12} is a group of the formula: $-Z_1-R_{13}$ (Z_1 and R_{13} are as defined above); and may form, together with the adjacent nitrogen atom, a heterocycle having a skeleton consisting of 3 to 15 atoms and optionally having substituent(s) and attached by a secondary nitrogen atom forming its ring], or a salt thereof, and

[36] a prodrug of the compound of [35].

Best Mode for Embodying the Invention

[0008] In the above-mentioned formula, the heterocycle group, represented by R_1 or R_9, has a skeleton consisting of 3 to 15 atoms including 1 to 5 nitrogen atom(s), and may be a monocyclic or fused ring and may be saturated or unsaturated. It is limited to a ring having a structure wherein a nitrogen atom constituting the heterocycle can have a bond, which is a ring having a secondary nitrogen atom.

[0009] As such heterocycle, (1) monocyclic heterocycles such as (a) aziridine, azetidine, pyrrole, 2- or 3-pyrroline, pyrrolidine, pyrazole, 2-, 3- or 4-pyrazoline, pyrazolidine, imidazole, 2-, 3- or 4-imidazoline, imidazolidine or (b) structurally possible hydrides of oxazole, isoxazole, thiazole, isothiazole, various oxadiazoles, various thiadiazoles, pyridine, pyridazine, pyrimidine or pyrazine; monocyclic heterocycle such as morpholine, thiomorpholine and the like, (2) fused heterocycles such as (a) indole, isoindole, indazole or purine and structurally possible hydrides thereof, (b) structurally possible hydrides of quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cincholine or pteridine, (c) carbazole or carboline and structurally possible hydrides thereof, (d) structurally possible hydrides of phenanthridine, acridine, phenanthroline or phenazine, (e) phenothiazine or phenoxazine and structurally possible hydrides thereof and the like, and the like are used. Of these, pyrrole, pyrrolidine, pyrazole, pyrazolidine, imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, piperidine, piperazine, morpholine, thiomorpholine, indole, indoline, isoindole, isoindoline, indazole, 2,3-dihydroindazole, purine, 1,2,3,4-tetrahydroquinoline and the like are preferable, particularly indoline is preferable.

[0010] The heterocycle group represented by R_1 or R_9, which has a skeleton consisting of 3 to 15 atoms including 1 to 5 nitrogen atom(s), may be substituted by 1 to 5 the same or different substituent(s), as long as it is structurally possible. As such substituent(s), for example, C_{1-8} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, hexyl, heptyl, octyl and the like, preferably C_{1-6} alkyl), C_{2-8} alkenyl (e.g., ethenyl, propenyl, butenyl, pentenyl and the like, preferably C_{2-6} alkenyl), C_{2-8} alkynyl (e.g., ethynyl, propinyl, butyryl, pentinyl and the like, preferably C_{2-6} alkynyl), C_{7-16} aralkyl (e.g., benzyl, phenethyl and the like), C_{3-8} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like, preferably C_{3-6} cycloalkyl), C_{3-8} cycloalkenyl (e.g., cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl and the like, preferably C_{3-6} cycloalkenyl), C_{6-14} aryl (e.g., phenyl, naphthyl and the like), C_{1-8} alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, t-butoxy, pentoxy and the like, preferably C_{1-6} alkoxy), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy and the like, preferably methylenedioxy), hydroxy, halogen atom (fluorine, chlorine, bromine, iodine), amino, (di or mono-C_{1-5} alkyl)amino (e.g., methylamino, dimethylamino, etholamino, diethylamino and the like), (C_{1-5} alkoxy-carbonyl)amino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino and the like), (C_{1-3} acyl)amino (e.g., formylamino, acetylamino, ethylcarbonylamino and the like), (C_{1-5} acyl) (C_{1-5} alkyl)amino (e.g., formylmethylamino, acetylmethylamino, formylethylamino, acetylethylamino and the like), C_{1-5} alkylthio (e.g., methylthio, ethylthio and the like), nitrile, nitro, C_{1-5}alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and the like), carboxyl, C_{1-5} alkyl-carbonyloxy (e.g., methylcarbonyloxy, ethylcarbonyloxy and the like), oxo, thioxo, C_{1-6} acyl group (e.g., C_{1-5} alkyl-carbonyl group such as acetyl, ethylcarbonyl, propylcarbonyl and the like, and the like), sulfamoyl, (di or mono-C_{1-5} alkyl)sulfamoyl (e.g., methylsulfamoyl, ethylsulfamoyl, dimethylsulfamoyl and the like) and the like are used.

[0011] The above-mentioned C_{1-8} alkyl and C_{1-8} alkoxy may be further substituted by 1 to 5 the same or different substituent(s) selected from the above-mentioned C_{1-8} alkoxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl) amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl)(C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo and the like, as long as it is structurally possible.

[0012] Of the above-mentioned substituents, optionally halogenated C_{1-5} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, trifluoromethyl and the like), C_{1-3} alkoxy (e.g., methoxy, ethoxy, propoxy and the like), C_{1-2} alkylenedioxy, halogen atom and the like are preferable, particularly, optionally halogenated C_{1-3} alkyl such as methyl, ethyl, trifluoromethyl and the like, and halogen atom such as fluorine, chlorine, bromine and the like are more preferable.

[0013] In the above-mentioned formula, X and X_2 are oxygen atom, nitrogen atom optionally substituted by C_{1-5} alkyl (e.g., methyl, ethyl, propyl, butyl and the like) or a sulfur atom optionally oxidized with 1 or 2 oxygen (S, SO, SO_2).

[0014] As X and X_2, oxygen atom and NH are preferable, particularly oxygen atom is preferable.

[0015] In the above-mentioned formula, Y and Y_1 represent a bond or C_{1-5} alkylene group (e.g., methylene, ethylene, propylene, butylene and the like).

[0016] As Y and Y_1, C_{1-3} alkylene group such as methylene, ethylene, propylene and the like are preferable, particularly methylene is preferable.

[0017] In the above-mentioned formula, R_{10} represents (1) hydrogen atom, (2) hydroxy group, (3) C_{1-5} alkoxy group, (4) C_{1-5} alkylthio group, (5) carbocycle having 3 to 15 carbon atoms or (6) heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s).

[0018] In the above-mentioned formula, R_2 is (1) hydrogen atom, (2) hydroxy group, (3) C_{1-5} alkoxy group, (4) C_{1-5} alkylthio group, (5) carbocycle having 3 to 15 carbon atoms or (6) heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) (provided that when Y is a bond, R_2 is a carbocycle having 3 to 15 carbon atoms

or a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s)).

[0019] As the C_{1-5} alkoxy group represented by R_2 or R_{10}, for example, methoxy, ethoxy, propoxy, butoxy, t-butoxy, pentoxy and the like are used, with preference given to C_{1-3} alkoxy such as methoxy, ethoxy, propoxy and the like, and the like.

[0020] As the C_{1-5} alkylthio group represented by R_2 or R_{10}, for example, methylthio, ethylthio, propylthio and the like are used, with preference given to C_{1-3} alkylthio group and the like.

[0021] As the carbocycle group having 3 to 15 carbon atoms, which is represented by R_2 or R_{10}, for example, (1) saturated or unsaturated monocyclic aliphatic hydrocarbon group such as C_{3-8} cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), C_{5-8} cycloalkenyl group (e.g., cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl) and the like, (2) saturated or unsaturated fused ring aliphatic hydrocarbon group having 9 to 15 carbon atoms or (3) monocyclic or polycyclic aryl group having 6 to 15 carbon atoms (e.g., phenyl, naphthyl, indenyl, phenanthrenyl, indenyl, indanyl, tetralinyl and the like) and the like are used. Of these, cyclopentyl, cyclohexyl, cycloheptenyl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 3-cyclohexen-1-yl, phenyl, naphthyl, indenyl, phenanthrenyl, indenyl, indanyl, tetralinyl and the like are preferable, particularly, phenyl is preferable.

[0022] As the heterocycle group having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s), which is represented by R_2 or R_{10}, for example, an aromatic heterocycle group or saturated or unsaturated non-aromatic heterocycle group having a skeleton consisting of 3 to 15 atoms including 1 to 5, the same or different nitrogen atom (s), oxygen atom(s) and/or sulfur atom(s), and the like are used.

[0023] As the above-mentioned aromatic heterocycle group, for example, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isooxazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthidinyl, quinoxalinyl, quinazolinyl, cinnolinyl, puteridinyl, carbazolyl, carbolinyl, phenanthridinyl, acrydinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxadinyl and the like, and if structurally possible, a group wherein these are fused with a benzene ring, and the like are used. Particularly, an aromatic heterocycle group having a skeleton consisting of 5 or 6 atoms including 1 to 3 (preferably 1 or 2) heteroatom(s) such as nitrogen atom(s), oxygen atom(s) and sulfur atom(s), such as furyl, thienyl, pyridyl and the like, and the like are preferable.

[0024] As the above-mentioned saturated or unsaturated non-aromatic heterocycle group, for example, structurally possible partial or complete hydrides of the above-mentioned aromatic heterocycle group, aziridinyl, azetidinyl, oxetanyl, pyranyl, azepinyl, 1,3-diazepinyl, 1,4-diazepinyl, 1,3-oxazepinyl, 1,4-oxazepinyl, azocinyl, chromenyl and the like, and structurally possible hydrides thereof and the like are used.

[0025] The carbocycle having 3 to 15 carbon atoms and the heterocycle group having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s), which are represented by R_2 or R_{10}, may be substituted by 1 to 5 the same or different substituent(s) as long as it is structurally possible. As these substituents, those similar to the substituents of the aforementioned heterocycle group represented by R_1 are used.

[0026] Of these substituents, optionally halogenated C_{1-8} alkyl (particularly, optionally halogenated C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, trifluoromethyl and the like, particularly, optionally halogenated C_{1-3} alkyl), C_{1-8} alkoxy (preferably C_{1-6} alkoxy such as methoxy, ethoxy and the like, particularly C_{1-3} alkoxy), halogen atom such as fluorine, chlorine, bromine and the like, and the like are preferable.

[0027] As R_{10}, hydrogen atom, hydroxy group, C_{1-5} alkoxy group, C_{1-5} alkylthio group, the above-mentioned carbocycle having 3 to 15 carbon atoms or a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and the like are preferable.

[0028] As R_2, the above-mentioned carbocycle having 3 to 15 carbon atoms or a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and the like are preferable.

[0029] When Y is C_{1-5} alkylene group, hydrogen atom, hydroxy group, C_{1-5} alkoxy group, C_{1-5} alkylthio group and the like are also preferable as R_2, and particularly when Y is methylene group, hydrogen atom, C_{1-5} alkoxy group, C_{1-5} alkylthio group and the like are also preferable as R_2.

[0030] In the above-mentioned formula, R_3 and R_4 are the same or different and each is hydrogen atom or a group of the formula: $-Z-R_5$.

[0031] In the above-mentioned formula, R_{11} and R_{12} are the same or different and each is hydrogen atom or a group of the formula: $-Z_1-R_{13}$.

[0032] Z and Z_1 show a bond or C_{1-10} alkylene group (e.g., methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene and the like, preferably C_{1-6} alkylene group).

[0033] The C_{1-10} alkylene group represented by Z or Z_1 may be substituted by 1 to 5 substituent(s) as long as it is structurally possible. As such substituents, those similar to the substituents of the aforementioned heterocycle group represented by R_1 are used.

[0034] As Z and Z_1, for example, a bond, C_{1-4} alkylene (e.g., methylene, ethylene, propylene, butylene) and the like are preferable.

[0035] As (1) a carbocycle having 3 to 15 carbon atoms and (2) a heterocycle having a skeleton consisting of 3 to

15 atoms including 1 to 5 heteroatom(s), which are represented by R_5 or R_{13}, those similar to (1) a carbocycle having 3 to 15 carbon atoms and (2) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom (s), which are represented by R_2, are used.

[0036] Particularly, as a carbocycle group having 3 to 15 carbon atoms represented by R_5 or R_{13}, for example, a non-aromatic carbocyclic ring group having 3 to 7 carbon atoms such as cyclopropyl, cyclobutyl, cyclocyclopentyl, cyclohexyl, cycloheptenyl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 3-cyclohexen-1-yl and the like, and an aromatic carbocyclic ring group having 6 to 15 carbon atoms such as phenyl, naphthyl, indenyl, phenanthrenyl, indenyl, indanyl, tetralinyl and the like are preferable, which is particularly preferably C_{6-14} aryl group such as phenyl and the like.

[0037] As the heterocycle group having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) represented by R_5 or R_{13}, for example, non-aromatic heterocycle group such as azetidinyl, pyrrolizinyl, piperidinyl, piperazinyl, perhydroazepinyl, morphonyl, tetrahydrofuranyl, tetrahydrothienyl and the like, and an aromatic heterocycle group such as pyridin-2-yl, pyridin-3-yl, pyrazin-2-yl, perhydroazepin-3-yl and the like are preferable.

[0038] As long as structurally possible, (1) a carbocycle having 3 to 15 carbon atoms and (2) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s), which are represented by R_5 or R_{13}, may have substituent(s) such as those similar to the substituent(s) of the aforementioned heterocycle group represented by R_1.

[0039] Of these substituents, optionally halogenated C_{1-8} alkyl (particularly optionally halogenated C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, trifluoromethyl and the like), C_{1-8} alkoxy (particularly C_{1-6} alkoxy such as methoxy, ethoxy, propoxy, isopropyloxy, butoxy, sec-butoxy, t-butoxy and the like), halogen atom (fluorine, chlorine, bromine, iodine), oxo, thioxo, hydroxy, nitrile, C_{1-5} alkylthio (particularly C_{1-3} alkylthio such as methylthio, ethylthio and the like), carbamoyl, C_{1-5} alkoxy-carbonyl group (particularly, methoxycarbonyl, ethoxycarbonyl and the like), C_{1-6} acyl group (particularly C_{1-5} alkyl-carbonyl group such as acetyl, ethylcarbonyl, propylcarbonyl and the like), and the like, sulfamoyl and the like are preferably, particularly C_{1-8} alkyl, C_{1-8} alkoxy, halogen atom such as fluorine, chlorine, bromine and the like, oxo, thioxo and the like are preferable.

[0040] Furthermore, R_5 and R_{13} respectively show hydrogen atom; hydroxy group; C_{1-5} alkoxy group such as methoxy, ethoxy and the like; nitrile group; C_{1-5} alkoxy-carbonyl group such as methoxycarbonyl, ethoxycarbonyl, propylcarbonyl, butylcarbonyl, t-butoxycarbonyl and the like; carboxyl group; carbamoyl group; (mono or di-C_{1-5} alkyl)carbamoyl group such as methylaminocarbonyl, diethylaminocarbonyl and the like; amino group; (di or mono-C_{1-5} alkyl) amino group such as methylamino, diethylamino and the like; methoxycarbonylamino; ethoxycarbonylamino; propoxycarbonylamino; butoxycarbonylamino; C_{1-5} alkylthio group such as methylthio and the like, and are respectively bonded to the adjacent Z and Z_1 at a substitutable position.

[0041] Particularly when Z is optionally substituted C_{2-10} alkylene group, preferably the aforementioned carbocyclic ring or heterocycle, hydrogen atom, hydroxy group, C_{1-5} alkoxy group such as methoxy, ethoxy and the like, nitrile group, C_{1-5} alkoxy-carbonyl group such as methoxycarbonyl, ethoxycarbonyl, propylcarbonyl, butylcarbonyl, t-butoxycarbonyl and the like, carboxyl group, carbamoyl group, (mono or di-C_{1-5} alkyl)carbamoyl group such as methylaminocarbonyl, diethylaminocarbonyl and the like, amino group, (di or mono-C_{1-5} alkyl)amino group such as methylamino, diethylamino and the like, methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, C_{1-5} alkylthio group such as methylthio and the like, and the like are also preferable as R_5. Particularly, hydroxy group, nitrile group, C_{1-5} alkoxy-carbonylamino group such as t-butoxycarbonylamino and the like, C_{1-5} alkoxy-carbonyl group such as methoxycarbonyl, t-butoxycarbonyl and the like, and the like are preferable.

[0042] When Z is optionally substituted methylene group, R_5 is, besides the aforementioned carbocyclic ring and heterocycle, nitrile group, C_{1-5} alkoxy-carbonyl group such as methoxycarbonyl, t-butoxycarbonyl and the like, carboxyl group, carbamoyl group, (mono or di-C_{1-5} alkyl)carbamoyl such as methylaminocarbonyl, diethylaminocarbonyl and the like, and the like are preferable, particularly nitrile group is preferable.

[0043] As R_{13}, besides the aforementioned carbocyclic ring and heterocycle, hydroxy group, nitrile group, C_{1-5} alkoxy-carbonylamino group such as t-butoxycarbonylamino and the like, C_{1-5} alkoxy-carbonyl group such as methoxycarbonyl, t-butoxycarbonyl and the like, and the like are also preferable.

[0044] As the combination of R_3 and R_4, that wherein R_3 is a hydrogen atom and R_4 is a group of the formula: $-Z-R_5$ is preferable.

[0045] As the combination of R_{11} and R_{12}, that wherein R_{11} is a hydrogen atom and R_{12} is a group of the formula: $-Z_1-R_{13}$ is preferable.

[0046] As the group which is a heterocycle having a skeleton consisting of 3 to 15 atoms and formed by R_3 and R_4, or R_{11} and R_{12}, together with the adjacent nitrogen atom, and which is attached by a secondary nitrogen atom forming the heterocycle, a group attached by a secondary nitrogen atom constituting a heterocycle having a skeleton consisting of 3 to 15 atoms including atoms such as carbon atom(s), oxygen atom(s), sulfur atom(s) and the like, besides at least one nitrogen atom, is used, which is, for example, aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, indolin-1-yl and the like. Particularly, a heterocycle having a skeleton consisting of 5 or 6 atoms including atoms such as carbon atom(s), oxygen atom(s), sulfur atom(s) and the like, besides at least one nitrogen atom, and attached by a secondary nitrogen atom is preferable, such as pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino and

the like.

[0047] The heterocycle having a skeleton consisting of 3 to 15 atoms and attached by a secondary nitrogen atom forming its ring, which is formed by R_3 and R_4, or R_{11} and R_{12} together with the adjacent nitrogen atom, may have substituents such as those similar to the substituents of the aforementioned heterocycle group represented by R_1.

[0048] Of these substituents, hydroxy group, nitrile group, C_{1-5} alkoxy-carbonyl group such as methoxycarbonyl, t-butoxycarbonyl and the like, and the like are preferable.

[0049] As the compound (I') of the present invention, the compound (I) of the present invention, and the like are preferable.

[0050] As the compound (I) of the present invention, for example, the following compound and the like are also preferable.

(1) Compound (I) wherein X is a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom(s) or a sulfur atom optionally oxidized with 1 or 2 oxygen.

(2) Compound (I) wherein Y is C_{1-5} alkylene group.

(3) Compound (I) wherein Y is C_{1-5} alkylene group, and R_2 is hydroxy group, C_{1-5} alkoxy group or C_{1-5} alkylthio group.

(4) Compound (I) wherein R_5 is (a) a non-aromatic carbocycle having 3 to 15 carbon atoms or (b) a non-aromatic heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s).

(5) Compound (I) wherein Z is C_{2-10} alkylene group optionally having substituent(s), R_5 is hydroxy group, nitrile group, C_{1-5} alkoxy-carbonyl, carboxyl group, carbamoyl group, (mono or di-C_{1-5} alkyl)carbamoyl group, (C_{1-5} alkoxy-carbonyl)amino group or C_{1-5} alkylthio group.

(6) Compound (I) wherein Z is methylene group optionally having substituent(s), and R_5 is nitrile group, C_{1-5} alkoxy-carbonyl group, carboxyl group, carbamoyl group or (mono or di-C_{1-5} alkyl)carbamoyl group.

(7) Compound (I) wherein the substituent(s) of heterocycle and a carbocycle having 3 to 15 carbon atoms are selected from the group consisting of C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-3} alkylenedioxy, hydroxy, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo and thioxo.

(8) Compound (I) wherein R_1 is a heterocycle having a skeleton consisting of 5 to 12 atoms including 1 or 2 nitrogen atom(s), which is optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl) amino, (C_{1-5} alkoxy-carbonyl) amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo and thioxo.

(9) Compound (I) wherein R_1 is a heterocycle having a skeleton consisting of 8 to 12 atoms including a nitrogen atom, which is optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo and thioxo.

(10) Compound (I) wherein R_1 is 1-indolinyl optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl) amino, (C_{1-5} acyl)amino, (C_{1-5} acyl)(C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo and thioxo.

(11) Compound (I) wherein R_2 is a carbocycle having 5 to 7 carbon atoms or a heterocycle having a skeleton consisting of 5 to 7 atoms including 1 or 2 heteroatom(s), which is optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl) amino, (C_{1-5} alkoxy-carbonyl) amino, (C_{1-5} acyl) amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo and thioxo.

(12) Compound (I) wherein R_2 is phenyl optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl) amino, (C_{1-5} acyl)amino, (C_{1-5} acyl)(C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl.

(13) Compound (I) wherein X is oxygen atom or NH, and Y is C_{1-3} alkylene group.

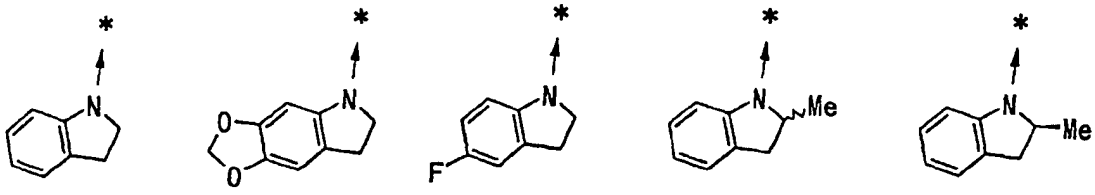
(14) Compound (I) wherein X is oxygen atom, and Y is methylene group.

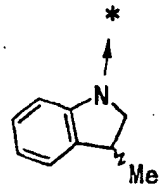
(15) Compound (I) wherein R_3 is hydrogen atom, and R_4 is a group of the formula: -Z-R_5.

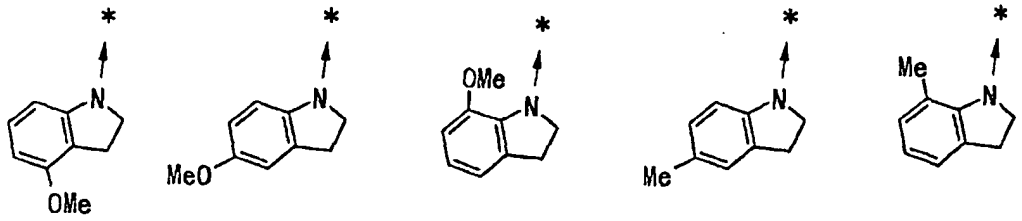
(16) Compound (I) wherein Z is a bond or C_{1-4} alkylene group, and R_5 is a carbocycle having 5 to 8 carbon atoms

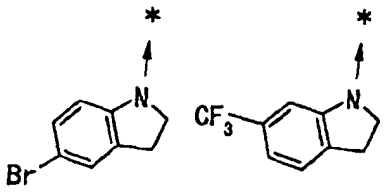
or a heterocycle having a skeleton consisting of 5 to 11 atoms including 1 to 5 hetero atom(s), which is optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl.

(17) Compound (I) wherein R_1 is a group selected from the group consisting of

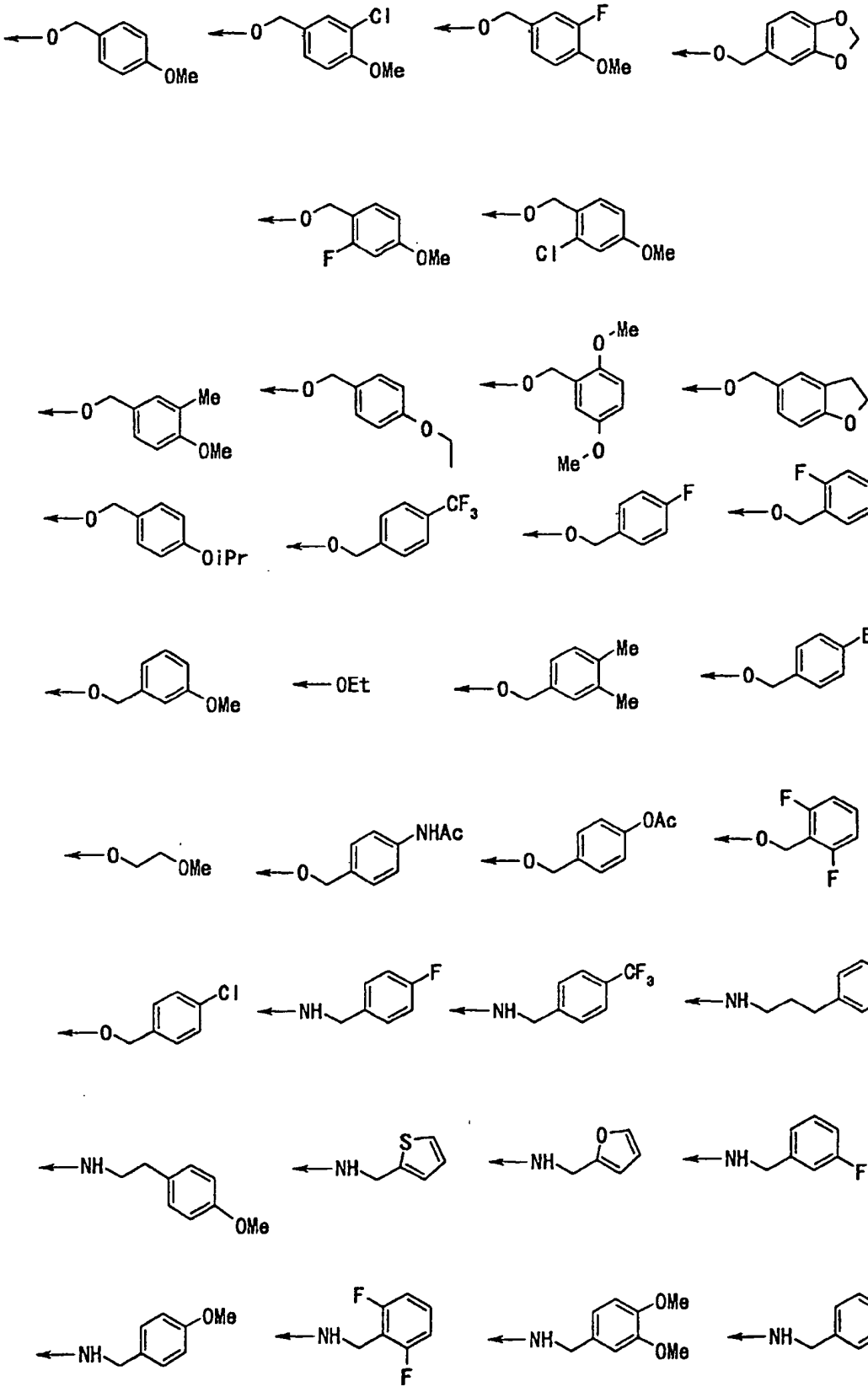


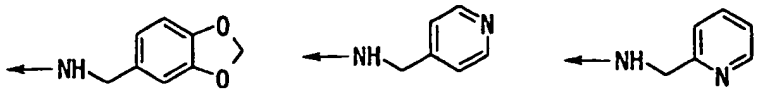




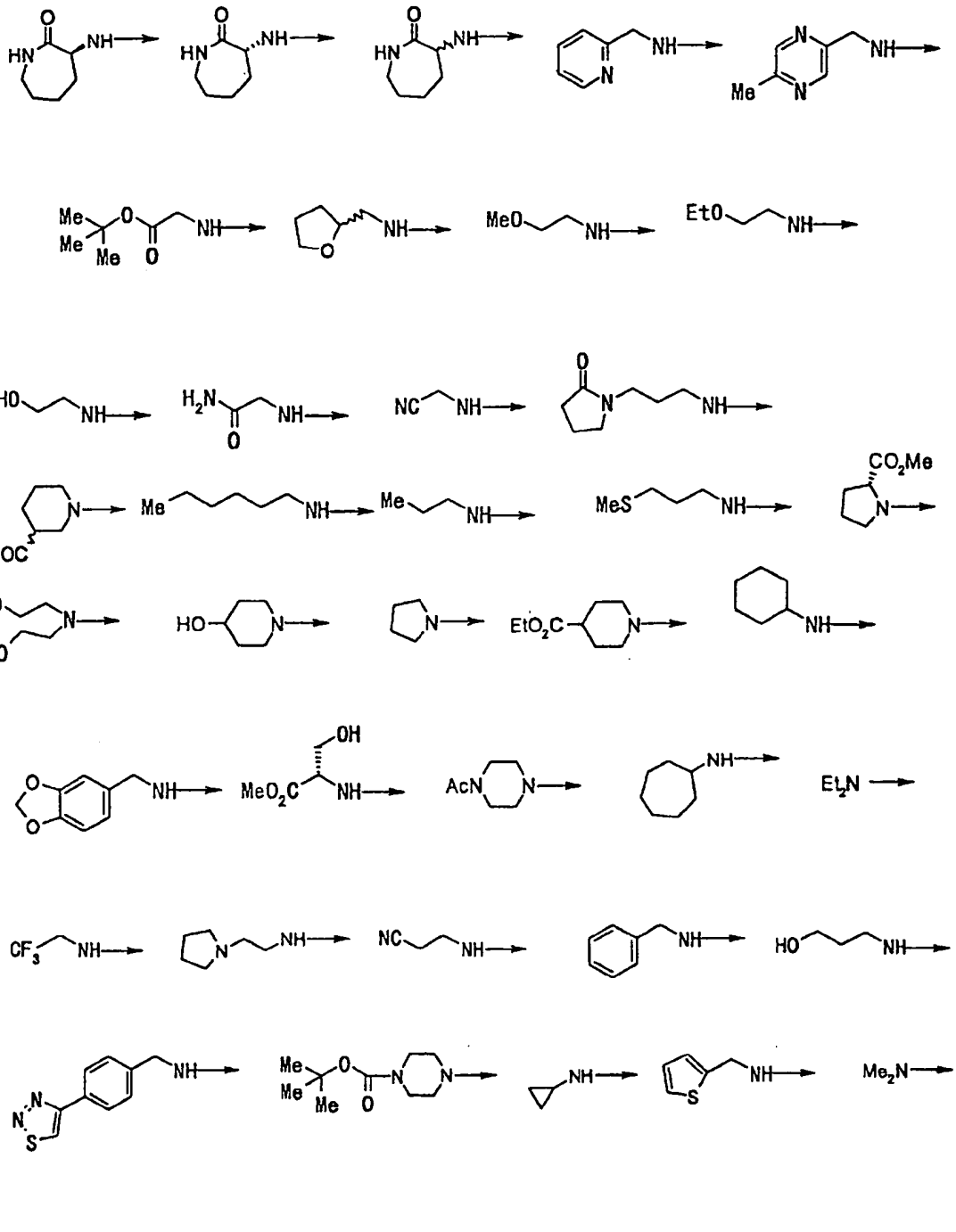


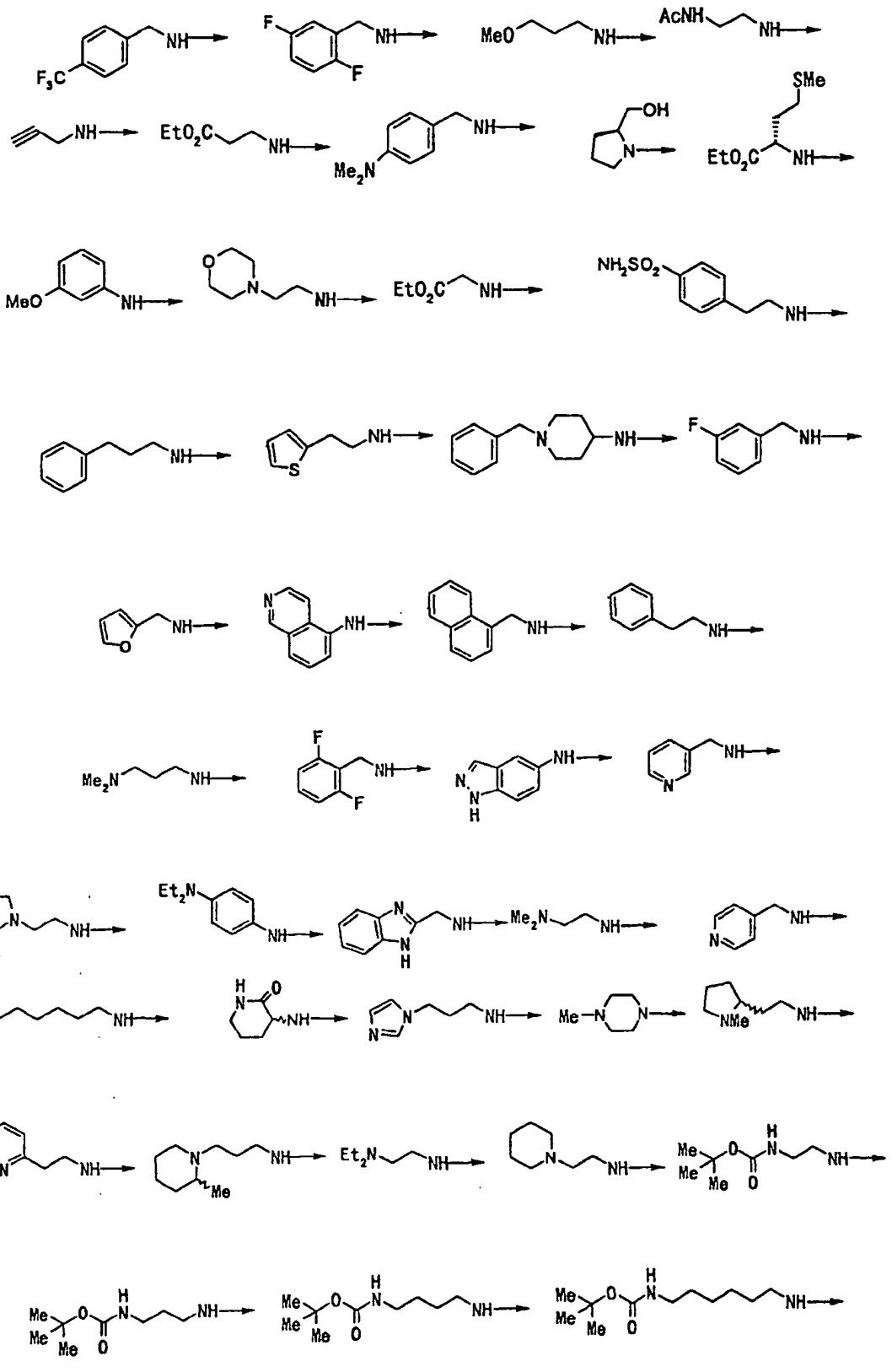
, -X-Y-R_2 is a group selected from the group consisting of



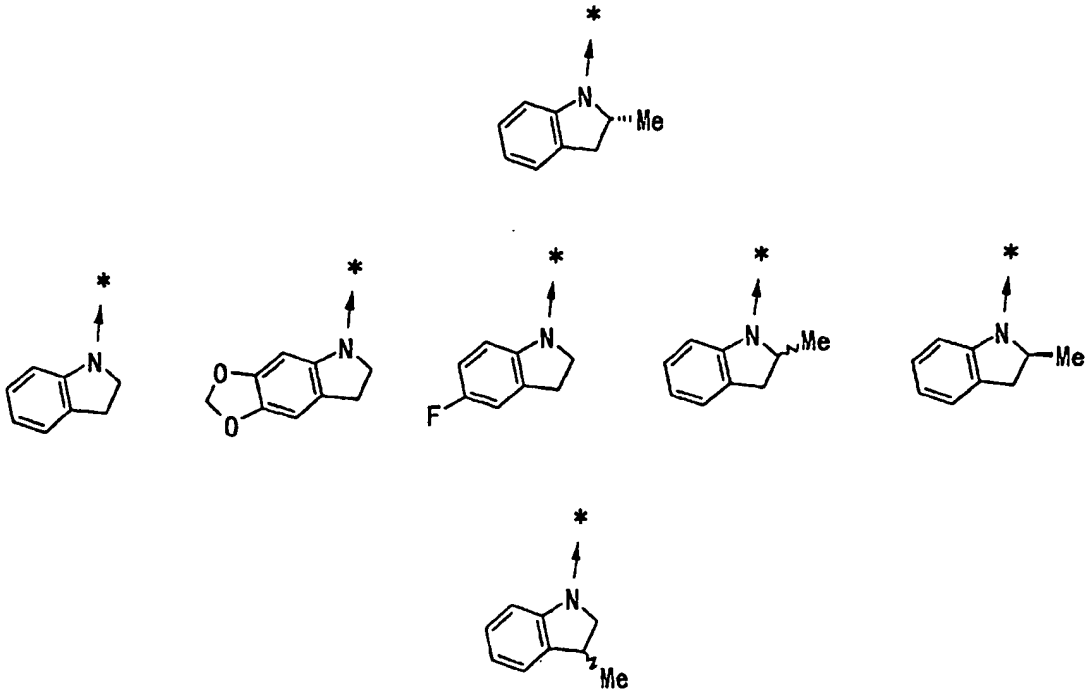


, and -NR_3R_4 is a group selected from the group consisting of

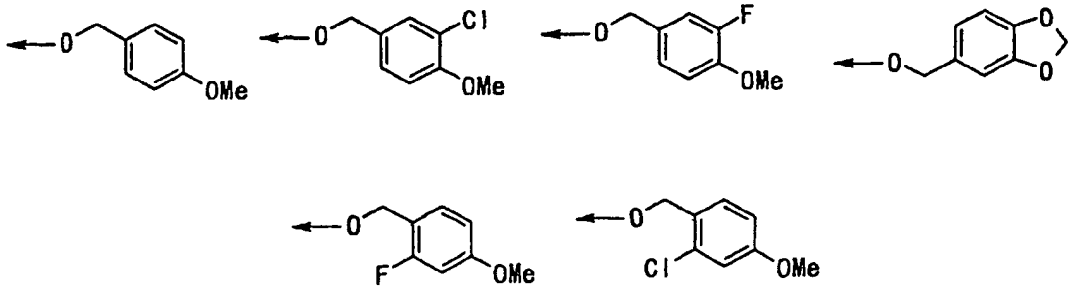




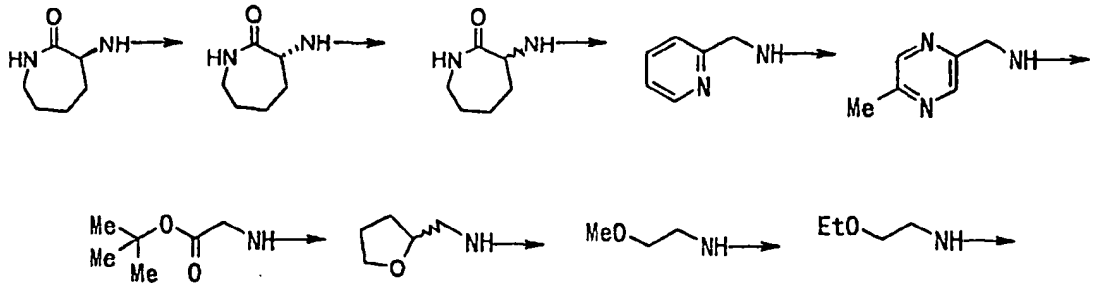
(18) Compound (I) wherein R_1 is a group selected from the group consisting of



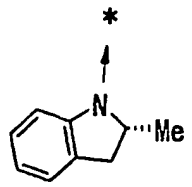
, -X-Y-R_2 is a group selected from the group consisting of



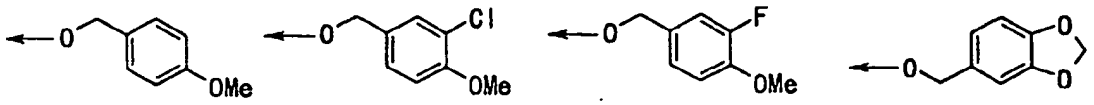
, and -NR_3R_4 is a group selected from the group consisting of



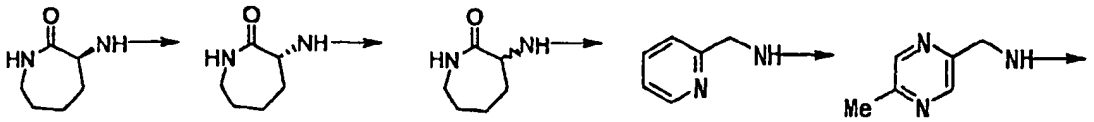
(19) Compound (I) wherein R_1 is a group selected from the group consisting of



, -X-Y-R_2 is a group selected from the group consisting of



, and -NR_3R_4 is a group selected from the group consisting of

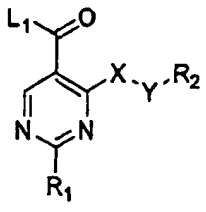


(20) Any compound produced in the Examples to be mentioned below.
(21) The following Example compounds:

Example 23-6: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide,
Example 23-11: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide,
Example 23-16: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide,
Example 27-1: (RS)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide,
Example 27-4: 4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide,
Example 31-3: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide,
Example 31-5: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide,
Example 31-6: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide,
Example 33-3: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide,
Example 33-5: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide,
Example 33-6: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide,
Example 47-3: (rac)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide,
Example 66-1: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide,
Example 66-2: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide,
Example 66-3: 4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide,
Example 66-6: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-

5-pyrimidinecarboxamide,
Example 66-8: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide,
Example 66-11: 4-[(4-methoxybenzyl)oxy]-2-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide,
Example 66-12: 4-[(4-methoxybenzyl)oxy]-2-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide,
Example 66-14: 4-[(4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide,
Example 66-15: 4-[(4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide,
Example 66-16: 2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide,
Example 66-17: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide,
Example 66-20: 4-[(4-methoxybenzyl)oxy]-2-[(2S)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide,
Example 66-21: 4-[(4-methoxybenzyl)oxy]-2-[(2S)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide, and salts thereof.

[0051] The compound (I) of the present invention and a salt thereof can be produced according to a known method or a similar method. For example, compound (I) or a salt thereof can be produced by reacting a compound of the formula



(II)

wherein L_1 is a leaving group and other symbols are as defined above, or a salt thereof, with an amine compound represented by R_3R_4NH (R_3 and R_4 are as defined above).

[0052] As the leaving group usable for L_1, a suitable group capable of leaving, which is generally used in the field of organic synthetic chemistry, can be employed [e.g., groups capable of leaving, as described in Compendium of Organic Synthetic Methods, vols. 1-7, John Wiley & Sons Inc. New York (1971-1992), and R.C. Larock, Comprehensive Organic Transformation, VCH, New York (1989) and the like].

[0053] Specific examples of L_1 include hydroxy, substituted hydroxy (e.g., C_{1-6} alkyloxy or C_{6-10} aryloxy, C_{1-6} alkyl-carbonyloxy or C_{6-10} aryl-carbonyloxy, C_{1-6} alkyloxy-carbonyloxy or C_{6-10} aryloxy-carbonyloxy, (di-C_{1-6} alkyl or di-C_{6-10} aryl)phosphonoxy, 4 to 8-membered heteroaryloxy optionally having 1 to 3 heteroatom(s) or dicarboxylic imidoxy and the like, wherein these alkyl group and aryl group are optionally substituted by 1 to 5 halogen atom, nitro, cyano and the like), substituted mercapto group (e.g., C_{1-6} alkylthio, C_{6-10} arylthio or 4 to 8-membered heteroarylthio optionally having 1 to 3 heteroatom(s) or C_{1-6} alkylcarbonylthio), halogen atom (fluorine, chlorine, bromine and the like), azide or cyano and the like, wherein the above-mentioned C_{1-6} alkyl and C_{6-10} aryl are optionally substituted by 1 to 5 halogen atom(s) (fluorine, chlorine, bromine and the like).

[0054] When reactive groups, such as amino, carboxy, hydroxy and the like, are contained, besides reaction points, in the structural formulas of compound (II) and R_3R_4NH, these groups may be protected by a suitable protecting group according to a conventional method. After reaction, these protecting groups may be removed according to a conventional method.

[0055] As such protecting groups, for example, those generally used in this field, which are described in T. W. Green and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons Inc. New York (1991) and the like, can be employed.

[0056] For a so-called amide bond forming reaction of compound (II) or a salt thereof and an amine compound represented by R_3R_4NH, a reaction known *per se* can be employed [for example, Izumiya et al., Peputidogousei no Kiso to Jikken (Basic and Experiment of Peptide Synthesis), Maruzen (1985) and R.C. Larock, Comprehensive Organic Transformation, VCH, New York (1989) and the like]. Some examples are given in the following. When L_1 is hydroxy,

a so-called coupling reagent is preferably used.

[0057] As such reagent, for example, N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIPCI), water-soluble carbodiimide (WSC, e.g., 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), carbonyldiimidazole, benzotriazolyl-N-hydroxytrisdimethylamino phosphonium hexafluorophosphorylate (Bop), diphenylphosphoryl azide (DPPA) and the like are used.

[0058] When carbodiimide is used as a coupling reagent, N-hydroxysuccinimide, 1-hydroxybenzotriazole and the like may be used as an additive. In addition, when L_1 is hydroxy, activated ester method with p-nitrophenyl ester, N-hydroxysuccinimide ester and the like, carboxylic acid activation methods such as mixed acid anhydride method using various carboxylic acids, various carbonic acids or various phosphoric acids or azide method and the like can be beneficially used.

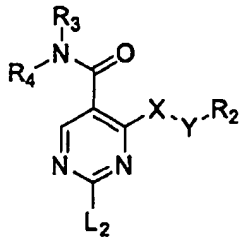
[0059] The reaction between compound (II) or a salt thereof and an amine compound represented by R_3R_4NH is generally carried out by agitation in an inert solvent.

[0060] The inert solvent to be used for the reaction is free of any particular limitation as long as the reaction is not adversely influenced. For example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, diethoxyethane, tetrahydrofuran and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; alkylnitriles such as acetonitrile, propionitrile and the like; nitroalkanes such as nitromethane, nitroethane and the like; and amides such as dimethylformamide, dimethylacetamide and the like are preferable.

[0061] A small amount of reeactable solvent (e.g., water, alcohol and the like) may be added depending on the property of the reactive group. While the reaction temperature varies depending on the starting material compound (II), amine compound represented by R_3R_4NH, the kind of additives, the kind of solvent and the like, it is generally from about -40°C to about 100°C, preferably from about -30°C to about 50°C. The reaction time is generally from about 1 minute to about 48 hours, preferably from about 15 minutes to about 24 hours.

[0062] The compound (II) and a salt thereof can be produced easily according to a known reaction or a similar reaction [e.g., Katritzky et al. ed., Comprehensive Heterocyclic Chemistry, vol. 3, and Brown et al. ed., The Pyrimidines, The Chemistry of Heterocyclic Compounds, vols. 16 and 52, John Wiley & Sons Inc., New York (1962 and 1994) and the like]. The compound represented by R_3R_4NH may be a commercially available compound as it is or can be produced easily according to a known reaction or a similar reaction.

[0063] The compound (I) of the present invention or a salt thereof can be also produced by reacting a compound of the formula



(III)

wherein L_2 is a leaving group and other symbols are as defined above, or a salt thereof, with a compound of the formula: R_1-H (R_1 is as defined above).

[0064] As the leaving group usable for L_2, a suitable group capable of leaving, which is generally used in the field of organic synthetic chemistry, can be employed [e.g., groups capable of leaving, as described in Compendium of Organic Synthetic Methods, vols. 1-7, John Wiley & Sons Inc. New York (1971-1992), and R.C. Larock, Comprehensive Organic Transformation, VCH, New York (1989) and the like].

[0065] As the preferable L_2, the leaving group used for introducing an amino group into the 2-position of pyrimidine, as described in Brown et al. ed., The Pyrimidines, The Chemistry of Heterocyclic Compounds, vol. 52, John Wiley & Sons Inc., New York (1994) and the like can be used.

[0066] Specific examples of L_2 to be used include halogen atom such as fluorine, chlorine, bromine and the like, mercapto, C_{1-6} alkylthio, C_{6-10} arylthio or 4 to 8-membered heteroarylthio optionally having 1 to 3 heteroatom(s), hydroxy, C_{1-6} alkyloxy, C_{6-10} aryloxy, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, C_{1-6} alkylsulfinyl, C_{6-10} arylsulfinyl, thiocyanate, cyano, C_{1-6} alkylcarbonyloxy, C_{6-10}arylcarbonyloxy, or amino optionally mono or di-substituted with C_{1-6} alkyl or C_{6-10} aryl, and the like, wherein the above-mentioned C_{1-6} alkyl and C_{6-10} aryl are optionally substituted by 1 to 5 halogen atom(s) (fluorine, chlorine, bromine and the like).

[0067] When reactive groups, such as amino, carboxy, hydroxy and the like, are contained, besides reaction points, in the structural formulas of compound (III) and R_1-H, these groups may be protected by a suitable protecting group according to a conventional method. After reaction, these protecting groups may be removed according to a conven-

tional method.

[0068] As such protecting groups, for example, those generally used in this field, which are described in T. W. Green and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons Inc. New York (1991) and the like, can be employed.

[0069] For a so-called aromatic nucleophilic substitution reaction of compound (III) or a salt thereof and a secondary amine compound represented by R_1-H, a reaction known *per se* can be employed [for example, The Pyrimidines, The Chemistry of Heterocyclic Compounds, vol. 52, John Wiley & Sons Inc., New York (1994) and the like]. This reaction is generally carried out by agitation in or without a solvent.

[0070] The solvent to be used for the reaction is free of any particular limitation as long as the reaction is not adversely influenced. For example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, diethoxyethane, tetrahydrofuran and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; alkylnitriles such as acetonitrile, propionitrile and the like; nitroalkanes such as nitromethane, nitroethane and the like; amides such as dimethylformamide, dimethylacetamide and the like; alcohols such as methanol, ethanol and the like or water are preferable.

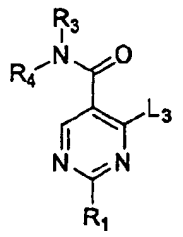
[0071] The reaction can be also carried out in the presence of a base, if necessary. Examples of the base include organic amines such as triethylamine, diisopropylethylamine and the like; basic inorganic salt such as sodium hydrogencarbonate, potassium carbonate and the like, and the like. This reaction can be also accelerated by the use of an acid catalyst. As such acid catalyst, for example, mineral acids such as hydrochloric acid, sulfuric acid and the like; organic acids such as trifluoroacetic acid, trifluoromethanesulfonic acid and the like; Lewis acids such as boron trifluoride, lanthanoide triflate and the like, and the like are used.

[0072] Particularly when L_2 is halogen, this reaction can be also accelerated by the use of palladium phosphine complex [e.g., combination of $Pd(dba)_2$ and tri-C_{1-6} alkylphosphine or tri-C_{6-10} arylphosphine and the like] as a catalyst.

[0073] While the reaction temperature varies depending on the starting material compound (III), a salt thereof, a secondary amine compound represented by R_1-H, the kind of additives, the kind of solvent and the like, it is generally from about 0°C to about 200°C, preferably from about 20°C to about 150°C. The reaction time is generally from about 1 minute to about 120 hours, preferably from about 15 minutes to about 72 hours.

[0074] The compound (III) and a salt thereof can be produced easily according to a known reaction or a similar reaction [e.g., Katritzky et al. ed., Comprehensive Heterocyclic Chemistry, vol. 3, and Brown et al. ed., The Pyrimidines, The Chemistry of Heterocyclic Compounds, vols. 16 and 52, John Wiley & Sons Inc., New York (1962 and 1994) and the like]. The compound represented by R_1-H may be a commercially available compound as it is or can be produced easily according to a known reaction or a similar reaction.

[0075] The compound (I) of the present invention or a salt thereof can be also produced by reacting a compound of the formula



(IV)

wherein L_3 is a leaving group and other symbols are as defined above, or a salt thereof, with a compound of the formula: R_2-Y-X_1-H (R_2, Y and X_1 are as defined above), and if desired, subjecting the resulting compound to oxidation.

[0076] As the leaving group usable for L_3, those similar to the leaving groups mentioned with regard to L_2 can be employed.

[0077] When reactive groups, such as amino, carboxy, hydroxy and the like, are contained, besides reaction points, in the structural formulas of compound (IV) and R_2-Y-X_1-H, these groups may be protected by a suitable protecting group according to a conventional method. After reaction, these protecting groups may be removed according to a conventional method.

[0078] As such protecting groups, for example, those generally used in this field, which are described in T. W. Green and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons Inc. New York (1991) and the like, can be employed.

[0079] For a so-called aromatic nucleophilic substitution reaction of compound (IV) or a salt thereof and a compound represented by R_2-Y-X_1-H, a reaction known *per se* can be employed [for example, The Pyrimidines, The Chemistry of Heterocyclic Compounds, vol. 52, John Wiley & Sons Inc., New York (1994) and the like]. This reaction is generally

carried out by agitation in or without a solvent.

[0080] The solvent to be used for the reaction is free of any particular limitation as long as the reaction is not adversely influenced. For example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, diethoxyethane, tetrahydrofuran and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; alkylnitriles such as acetonitrile, propionitrile and the like; nitroalkanes such as nitromethane, nitroethane and the like; amides such as dimethylformamide, dimethylacetamide and the like; alcohols such as methanol, ethanol and the like or water are preferable.

[0081] The reaction can be also carried out in the presence of a base, if necessary. Examples of the base include organic amines such as triethylamine, diisopropylethylamine and the like; basic inorganic salt such as sodium hydrogencarbonate, potassium carbonate and the like; metal hydrides such as sodium hydride, lithium hydride and the like, and the like.

[0082] This reaction can be also accelerated by the use of an acid catalyst. As such acid catalyst, for example, mineral acids such as hydrochloric acid, sulfuric acid and the like; organic acids such as trifluoroacetic acid, trifluoromethanesulfonic acid and the like; Lewis acids such as boron trifluoride, lanthanide triflate and the like, and the like are used.

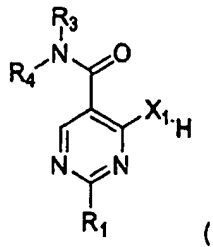
[0083] While the reaction temperature varies depending on the starting material compound (IV), a compound represented by R_2-Y-X_1-H, the kind of additives, the kind of solvent and the like, it is generally from about 0°C to about 200°C, preferably from about 20°C to about 150°C. The reaction time is generally from about 1 minute to about 120 hours, preferably from about 15 minutes to about 72 hours.

[0084] When X_1 is sulfur atom, a compound (I) wherein X is sulfone or sulfoxide, or a salt thereof, can be produced by producing compound (I) or a salt thereof under the above-mentioned conditions and the like, and oxidizing the compound.

[0085] As the oxidation used for this reaction, a reaction known *per se* [e.g., reaction described in Hudlicky, Oxidations in Organic Chemistry, The American Chemical Society (1990) and the like] can be used. Preferably, for example, it is a reaction using organic peracids such as benzoic acid, m-chlorobenzoic acid and the like, peroxides such as hydrogen peroxide, t-butyl hydroperoxide and the like, and the like.

[0086] The compound (IV) and a salt thereof can be produced easily according to a known reaction or a similar reaction [e.g., Katritzky et al. ed., Comprehensive Heterocyclic Chemistry, vol. 3, and Brown et al. ed., The Pyrimidines, The Chemistry of Heterocyclic Compounds, vols. 16 and 52, John Wiley & Sons Inc., New York (1962 and 1994) and the like]. The compound represented by R_2-Y-X_1-H may be a commercially available compound as it is or can be produced easily according to a known reaction or a similar reaction.

[0087] The compound (I) of the present invention can be also produced by reacting a compound of the formula



(V)

wherein X_1 is an oxygen atom, a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom(s) or a sulfur atom and other symbols are as defined above, or a salt thereof, with a compound represented by R_2-Y-L_4 (L_4 is leaving group and R_2 and Y are as defined above), and if desired, subjecting the resulting compound to oxidation.

[0088] As the leaving group usable for L_4, a suitable group capable of leaving, which is generally used in the field of organic synthetic chemistry, can be employed [e.g., groups capable of leaving, as described in Compendium of Organic Synthetic Methods, vols. 1-7, John Wiley & Sons Inc. New York (1971-1992), and R.C. Larock, Comprehensive Organic Transformation, VCH, New York (1989) and the like].

[0089] As L_4, for example, hydroxy, halogen atom (fluorine, chlorine, bromine and the like), substituted sulfonyloxy such as C_{1-6} alkanesulfonyloxy, C_{6-10} arenesulfonyloxy and the like are preferable, wherein C_{1-6} alkane and C_{6-10} arene are optionally substituted by 1 to 5 halogen atom(s) (fluorine, chlorine, bromine and the like).

[0090] When reactive groups, such as amino, carboxy, hydroxy and the like, are contained, besides reaction points, in the structural formulas of compound (V) and R_2-Y-L_4, these groups may be protected by a suitable protecting group according to a conventional method.

[0091] After reaction, these protecting groups may be removed according to a conventional method. As such pro-

tecting group, for example, those generally used in this field, which are described in T. W. Green and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons Inc. New York (1991) and the like, can be employed.

[0092] For a so-called nucleophilic substitution reaction of compound (V) or a salt thereof and a compound represented by R_2-Y-L_4, a reaction known per se can be employed [for example, reactions described in Comprehensive Organic Transformations, VCH, New York (1989) and the like]. To be specific, when, for example, L_4 is hydroxy, the conditions using a so-called Mitsunobu reagent (e.g., combination of diethyl azobiscarboxylate and triphenylphosphine and the like), and the like can be employed. When L_4 is halogen or substituted sulfonyloxy and the like, the reaction beneficially proceeds in the presence of a base.

[0093] As such base, organic amines such as triethylamine, diisopropylethylamine and the like; basic inorganic salt such as sodium hydrogencarbonate, potassium carbonate and the like; metal hydrides such as sodium hydride, lithium hydride and the like, and the like are used.

[0094] A so-called nucleophilic substitution reaction of compound (V) or a salt thereof and a compound represented by R_2-Y-L_4 is generally carried out by agitation in an inert solvent.

[0095] The inert solvent to be used for the reaction is free of any particular limitation as long as the reaction is not adversely influenced. For example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, diethoxyethane, tetrahydrofuran and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; alkylnitriles such as acetonitrile, propionitrile and the like; nitroalkanes such as nitromethane, nitroethane and the like; amides such as dimethylformamide, dimethylacetamide and the like; and mixed solvents thereof are preferable.

[0096] While the reaction temperature varies depending on the starting material compound (V), a compound represented by R_2-Y-L_4, the kind of additives, the kind of solvent and the like, it is generally from about -80°C to about 150°C, preferably from about -30°C to about 100°C. The reaction time is generally from about 1 minute to about 48 hours, preferably from about 15 minutes to about 24 hours.

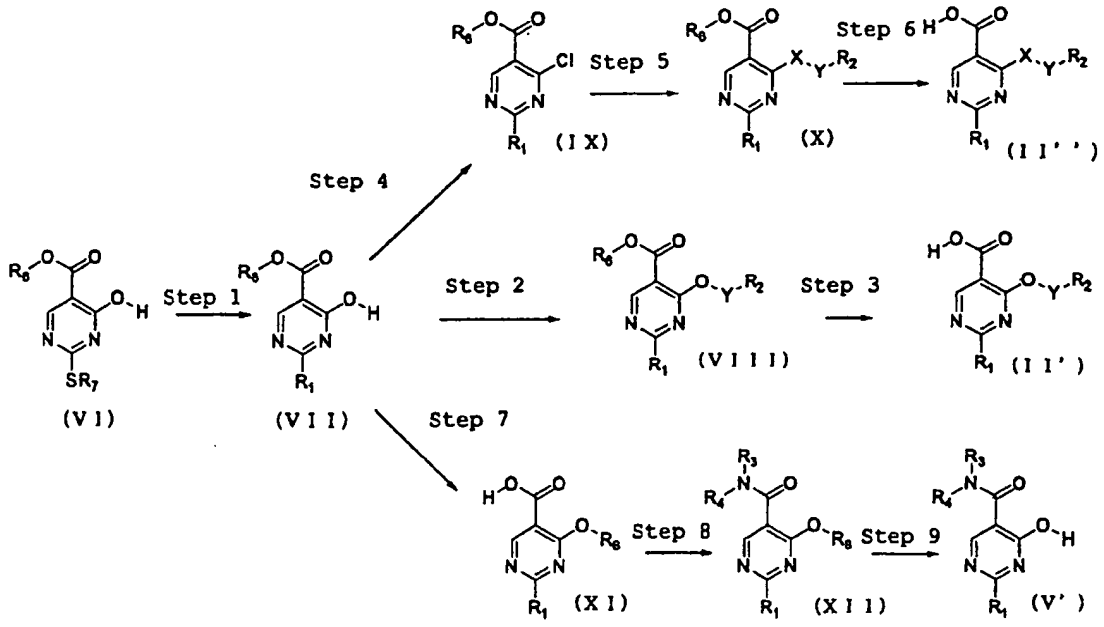
[0097] The compound (V) and a salt thereof can be produced easily according to a known reaction or a similar reaction [e.g., Katritzky et al. ed., Comprehensive Heterocyclic Chemistry, vol. 3, and Brown et al. ed., The Pyrimidines, The Chemistry of Heterocyclic Compounds, vols. 16 and 52, John Wiley & Sons Inc., New York (1962 and 1994) and the like]. The compound represented by R_2-Y-L_4 may be a commercially available compound as it is or can be produced easily according to a known reaction or a similar reaction.

[0098] The compound (I) of the present invention and a salt thereof can be produced by converting the substituents represented by R_1, X, Y, R_2, R_3 and R_4 of compound (I) to those represented by R_1, X, Y, R_2, R_3 and R_4, which are respectively different chemically. For such conversion of the substituents, a reaction known *per se* can be used. For example, reactions described in Comprehensive Organic Transformations, VCH, New York (1989) and the like can be employed.

[0099] The starting material compounds (II), (III), (IV) and (V) and salts thereof to be used in the present invention can be produced according to the above-mentioned known method or a method analogous thereto.

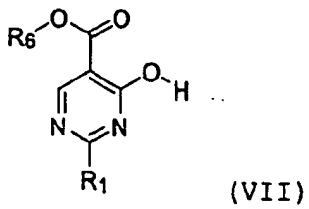
[0100] To be specific, for example, compounds (II'), (II") and (V') and salts thereof can be produced according to the method represented by the scheme 1 or a method analogous thereto.

Scheme 1



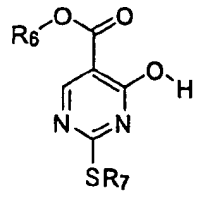
Step 1:

[0101] A compound of the formula



(VII)

wherein R_6 is a carboxyl-protecting group and R_1 is as defined above, can be produced by subjecting a compound of the formula



(VI)

wherein R_7 is C_{1-6} alkyl, C_{6-10} aryl or a 4 to 8-membered heteroaryl optionally having 1 to 3 heteroatom(s), wherein C_{1-6} alkyl and C_{6-10} aryl are optionally substituted by 1 to 5 halogen atom(s) (fluorine, chlorine, bromine and the like) and R_6 is as defined above, and a compound represented by R_1-H (R_1 is as defined above) to a method described in Production Method 2 or a method analogous thereto.

[0102] Particularly preferable reaction conditions are alcohols such as methanol, ethanol and the like as a solvent, reaction temperature of about 30 - about 120°C, and reaction time of from about 1 hour to about 48 hours.

[0103] In the formula (VI), as the carboxyl-protecting group represented by R_6, a protecting group generally used in the field of organic synthesis chemistry can be used [e.g., protecting groups described in Green and Wuts, Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons Inc., New York (1991) and the like].

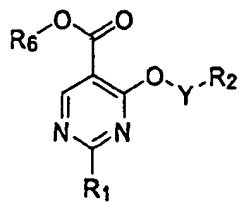
[0104] As particularly preferable carboxyl-protecting group represented by R_6, for example, an ester-forming protecting groups, such as methyl, ethyl, methoxymethyl, methoxyethoxymethyl, benzyloxymethyl, tert-butyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, o-nitrobenzyl, benzhydrile, trityl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, allyl and the like, are used.

[0105] In the formula (VI), as a group represented by R_7, C_{1-6} alkyl and C_{6-10} aryl are particularly preferable.

[0106] The compound (VI) and a salt thereof can be produced according to the method described in C.W. Todd et al., the Journal of The American Chemical Society, vol. 65, p. 350 (1943) or a method similar thereto.

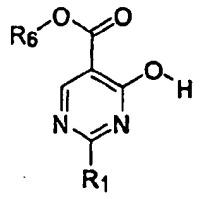
Step 2:

[0107] A compound represented by the formula



(VIII)

wherein each symbol is as defined above, can be produced by subjecting a compound represented by the formula



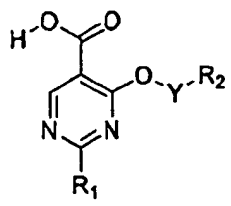
(VII)

wherein R_1 and R_6 are as defined above, and a compound represented by R_2-Y-L_4 (each symbol is as defined above) to the method described in Production Method 4 or a method similar thereto.

[0108] When L_4 is a halogen atom such as chlorine, bromine and the like, particularly preferable reaction conditions are the use of aromatic hydrocarbons such as benzene, toluene, xylene and the like, ethers such as diethoxyethane, tetrahydrofuran and the like or amides such as dimethylformamide, dimethylacetamide and the like as a solvent in the presence of basic inorganic salts such as sodium hydrogencarbonate, potassium carbonate and the like or metal hydrides such as sodium hydride, lithium hydride and the like, and the like at a reaction temperature of about -30 - about 100°C, and the reaction time of from about 0.5 hour to about 48 hours.

Step 3:

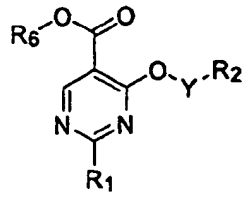
[0109] A compound represented by the formula



(II')

wherein the symbols in the formula are as defined above, can be produced by deprotecting the carboxylate residue

(-$COOR_6$) of the compound represented by the formula



(VIII)

wherein each symbol is as defined above.

[0110] The carboxyl-protecting group represented by R_6 can be removed under deprotection conditions generally employed in the field of organic synthesis chemistry [e.g., deprotection method described in Green and (Wuts), Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons Inc., New York (1991) and the like]. For example, a method using an acid, a method using a base, a method using reduction, a method using UV light, a method using a palladium complex, a method using a Lewis acid and the like can be mentioned.

[0111] Examples of preferable acid include organic acids such as formic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like; inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and the like, and the like, with which tert-butyl, p-methoxybenzyl, benzhydrile and the like are hydrolyzed.

[0112] Examples of preferable base include alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkaline earth metal hydroxides such as magnesium hydroxide, calcium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate and the like; alkaline earth metal carbonates such as magnesium carbonate, calcium carbonate and the like; alkali metal hydrogencarbonates such as sodium hydrogencarbonate, potassium hydrogencarbonate and the like; alkali metal acetates such as sodium acetate, potassium acetate and the like; alkaline earth metal phosphates such as calcium phosphate, magnesium phosphate and the like; alkali metal hydrogenphosphate such as disodium hydrogenphosphate, dipotassium hydrogenphosphate and the like, inorganic base such as aqueous ammonia and the like; organic base such as trimethylamine, triethylamine, diisopropylethylamine, pyridine, picoline, N-methylpyrrolidine, N-methylpiperidine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-en, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]-7-undecene and the like, and the like, with which methyl, ethyl and the like are hydrolyzed.

[0113] Examples of preferable reduction include reduction with sodium borohydride, reduction with zinc/acetic acid, catalytic reduction and the like, by which 2,2,2-trichloroethyl, benzyl, p-nitrobenzyl, benzhydrile and the like can be deprotected.

[0114] By the method using UV light, o-nitrobenzyl and the like can be deprotected.

[0115] By the method using palladium complex, allyl and the like can be deprotected.

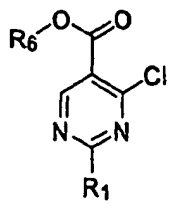
[0116] Examples of preferable Lewis acid include zinc chloride, zinc bromide, titanium tetrachloride, trimethylsilyl triflate and the like, with which methoxymethyl, 2-methoxyethoxymethyl, benzhydryl and the like can be deprotected.

[0117] The solvent for such deprotection is not particularly limited as long as it has no possibility of causing anything other than the objective reaction. For example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, diethoxyethane, tetrahydrofuran and the like; alcohols such as methanol, ethanol and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; alkylnitriles such as acetonitrile, propionitrile and the like; nitroalkanes such as nitromethane, nitroethane and the like; amides such as dimethylformamide, dimethylacetamide and the like; water or mixed solvents thereof are preferable.

[0118] While the reaction temperature varies depending on the starting material compound (VIII), deprotection conditions, the kind of solvent and the like, it is generally from about -80°C to about 150°C, preferably from about -30°C to about 100°C. The reaction time is generally from about 1 minute to about 72 hours, preferably from about 15 minutes to about 24 hours.

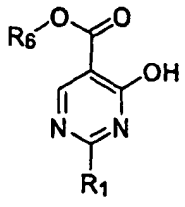
Step 4:

[0119] A compound represented by the formula



(IX)

wherein each symbol is as defined above, can be produced by converting hydroxy of a compound represented by the formula



(VII)

wherein each symbol is as defined above, to chlorine.

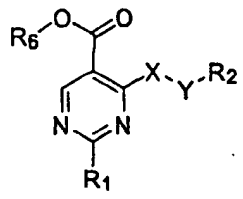
[0120] Such conversion reaction is described in detail in, for example , The Chemistry of Heterocyclic Compounds, vols. 16 and 52, John Wiley & Sons Inc., New York (1962 and 1994) and the like, and such methods or similar reactions can be employed.

[0121] It is preferable to carry out the reaction using phosphorus oxychloride as a chlorinating agent, without solvent at room temperature to boiling point temperature. The reaction time is generally from about 1 hour to about 24 hours.

[0122] In this Step, an example wherein hydroxy was converted to chlorine is shown. However, this Step is not particularly limited to the conversion to chlorine and a different leaving group may be employed for the next reaction. As such leaving group, a leaving group represented by L_3 can be employed, and a synthetic method thereof may be one described in the above-mentioned publications and the like.

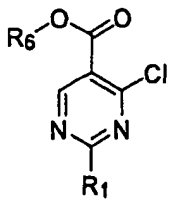
Step 5:

[0123] A compound represented by the formula



(X)

wherein the symbols in the formula are as defined above, can be produced by reacting a compound represented by



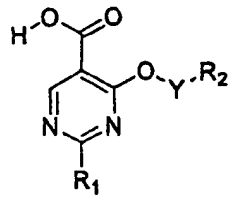
(IX)

wherein each symbol is as defined above, with a compound represented by R_2-Y-X_1-H (R_2, Y and X_1 are as defined above) under the conditions described in Production Method 3, whereafter subjecting the resulting compound to oxidation if necessary.

[0124] Preferable reaction conditions are reaction in the presence of basic inorganic salts such as sodium hydrogencarbonate, potassium carbonate and the like or metal hydrides such as sodium hydride, lithium hydride and the like, and the like, in aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethoxyethane, tetrahydrofuran and the like; amides such as dimethylformamide, dimethylacetamide and the like; alcohols such as methanol, ethanol, isopropanol and the like as a solvent, reaction temperature of from about -30°C to about 100°C, and the reaction time of from about 0.5 hour to about 48 hours.

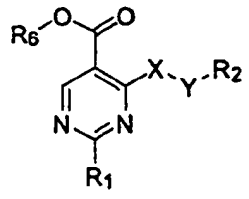
Step 6:

[0125] A compound represented by the formula



(II'')

wherein each symbol is as defined above, can be produced by deprotecting a carboxylic acid ester residue (-$COOR_6$) of the compound represented by the formula

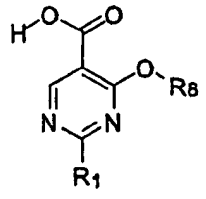


(X)

wherein each symbol is as defined above, under the same reaction conditions as in Step 3.

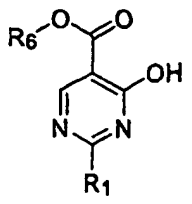
Step 7:

[0126] A compound represented by the formula



(XI)

wherein each symbol is as defined above, can be produced by protecting hydroxy of a compound represented by the formula



(VII)

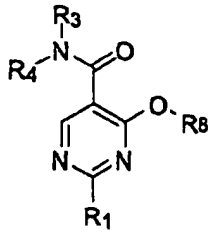
wherein each symbol is as defined above, by a protecting group R_8, and deprotecting the carboxylic acid residue ($-COOR_6$) under the same reaction conditions as in step 3.

[0127] As the hydroxy-protecting group represented by R_8, a protecting group generally used in the field of organic synthesis chemistry can be used [for example, protecting group described in Green and Wuts, Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons Inc., New York (1991) and the like]. Preferably, ether type protecting group such as benzyl, p-methoxybenzyl, p-nitrobenzyl, o-nitrobenzyl, benzhydrile, trityl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, allyl and the like; silyl ether type protecting group such as trimethylsilyl, tert-butyldimethylsilyl, diphenyl tert-butylsilyl and the like, and the like are used.

[0128] The method of introducing these protecting groups is described in detail in the above-mentioned publications and the like. Carboxylic acid ester residue ($-COOR_6$) can be deprotected under the same reaction conditions as in Step 3.

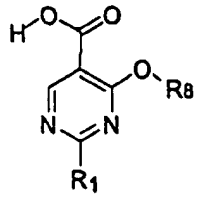
Step 8:

[0129] A compound represented by the formula



(XII)

wherein each symbol is as defined above, can be produced by reacting a compound represented by the formula

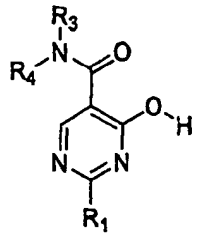


(XI)

wherein each symbol is as defined above, with an amine compound represented by R_3R_4NH wherein each symbol is as defined above, under the conditions described in Production Method 1.

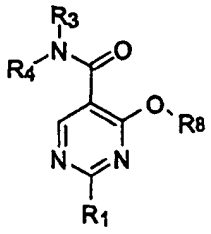
Step 9:

[0130] A compound represented by the formula



(V')

wherein each symbol is as defined above, can be produced by deprotecting a hydroxy-protecting group R_8 of a compound represented by the formula



(XII)

wherein each symbol is as defined above.

[0131] The hydroxy-protecting group R_8, can be removed under the deprotection conditions generally employed in the field of organic synthesis chemistry [for example, deprotection methods described in Green and Wuts, Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons Inc., New York (1991) and the like].

[0132] The compound (II) other than the above-mentioned compound (II') and (II"), compound (III), (IV) and compound (V) other than compound (V') can be produced according to a method similar to the above-mentioned or a combination of methods described in The Chemistry of Heterocyclic Compounds, vols. 16 and 52, John Wiley & Sons Inc., New York (1962 and 1994) and Comprehensive Organic Synthesis, vols. 1-9, Pergamon Press, Oxford (1991) and the like.

[0133] The compound (I) and a salt thereof of the present invention thus obtained can be isolated and purified by a known means, such as solvent extraction, solvent exchange, phase transfer, salting out, crystallization, recrystallization, chromatography and the like. When a protecting group is contained in the reaction product, the protecting group is removed if necessary by a typical method to give compound (I) or a salt thereof. In the field of organic synthesis chemistry, the protecting groups of amino, hydroxy and carboxy have been conventionally studied and methods of protection and deprotection have been established. These methods can be used for the production of the compound (I) of the present invention and synthetic intermediates thereof.

[0134] A reaction product obtained by the above-mentioned method, which contains the objective compound (I) or reaction product (I) obtained by other known methods may be obtained as an enantiomer or diastereomer mixture in some cases. Such mixture can be separated by fractional recrystallization, column chromatography and the like.

[0135] The compound (I') and a salt thereof of the present invention can be produced according to the above-mentioned production method of compound (I) of the present invention or a salt thereof.

[0136] The salts of compound (I) or (I') of the present invention are preferably pharmacologically acceptable. For example, salts with inorganic base, salts with organic base, salts with inorganic acid, salts with organic acid, salts with basic or acidic amino acid and the like are used.

[0137] Examples of preferable salts with inorganic base include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt and the like; aluminum salt, ammonium salt and the like.

[0138] Examples of preferable salts with organic base include trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like.

[0139] Examples of preferable salts with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like.

[0140] Examples of preferable salts with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

[0141] Examples of preferable salts with basic amino acid include salts with arginine, lysin, ornithine and the like,

examples of preferable salts with acidic amino acid include salts with aspartic acid, glutamic acid and the like.

[0142] It is also possible to convert compounds (I), (I') and salts thereof of the present invention to hydrate thereof according to a known method.

[0143] As the salts of the above-mentioned starting material compounds used for the production of compounds (I), (I') and salts thereof of the present invention, the same salts with the salts of compounds (I) and (I') are used.

[0144] The prodrug of compound (I), (I') or a salt thereof of the present invention may be a compound that converts to compound (I), (I') or a salt thereof due to the reaction of enzyme, gastric acid and the like under the physiological conditions in the body. That is, a compound that converts to compound (I), (I') or a salt thereof by enzymatic oxidation, reduction, hydrolysis and the like, and a compound that converts to compound (I), (I') or a salt thereof by hydrolysis and the like by gastric acid and the like.

[0145] A prodrug of compound (I), (I') or a salt thereof of the present invention is exemplified by a compound wherein an amino group of compound (I) or (I') is acylated, alkylated, phosphorylated (e.g., compound where amino group of compound (I) or (I') is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated and the like); compound wherein a hydroxy group of compound (I) or (I') is acylated, alkylated, phosphorinated, borated (e.g., compound where hydroxy group of compound (I) or (I') is acetylated, palmitoylated, propanoylated, pivaloylated, succinilated, fumarilated, alanilated, dimethylaminomethylcarbonylated and the like); compound wherein a carboxyl group of compound (I) or (I') is esterified or amidated (e.g., compound where carboxyl group of compound (I) or (I') is ethyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxymethyl esterified, ethoxycarbonyloxyethyl esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterified, cyclohexyloxycarbonyethyl esterified, methylamidated and the like) and the like. These compounds can be produced from compound (I) or (I') by a method known *per se*.

[0146] A prodrug of compound (I) or (I') may be a compound that converts to compound (I) or (I') under physiological conditions as described in Iyakuhin no Kaihatsu (Development of pharmaceutical products), vol. 7, Molecule Design, 163-198, Hirokawa Shoten (1990).

[0147] The compound (I), (I'), a salt thereof and a prodrug thereof (hereinafter sometimes to be simply referred to as the compound of the present invention) can be used safely as an agent for the prophylaxis or treatment of the diseases induced by promoted metabolism of cGMP.

[0148] The compound of the present invention can be admixed with a pharmaceutically acceptable carrier and orally or parenterally administered as a solid preparation such as tablet, capsule, granule, powder and the like; or a liquid preparation such as syrup, injection and the like.

[0149] Various organic or inorganic carriers conventionally used as materials for pharmaceutical preparations are used as a pharmacologically acceptable carrier, which is added as excipient, lubricant, binder, disintegrant for solid preparations; and solvent, dissolution aids, suspending agent, isotonicity agent, buffer, soothing agent and the like for liquid preparations. If necessary, additive for pharmaceutical preparations, such as preservative, antioxidant, coloring agent, sweetening agent and the like, can be also used.

[0150] Examples of preferable excipient include lactose, sucrose, D-mannitol, starch, crystalline cellulose, light silicic anhydride and the like.

[0151] Examples of preferable lubricant include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

[0152] Examples of preferable binder include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone and the like.

[0153] Examples of preferable disintegrant include starch, carboxymethylcellulose, calcium carboxymethylcellulose, sodium crosscarmellose, sodium carboxymethyl starch, and the like.

[0154] Examples of preferable solvent include water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, and the like.

[0155] Examples of preferable dissolution aids include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, Tris aminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, and the like.

[0156] Examples of preferable suspending agent include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, monostearic glyceride and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like.

[0157] Examples of preferable isotonicity agent include sodium chloride, glycerol, D-mannitol, and the like.

[0158] Examples of preferable buffer include phosphate buffer, acetate buffer, carbonate buffer, citrate buffer, and the like.

[0159] Examples of preferable soothing agent include benzyl alcohol and the like.

[0160] Examples of preferable preservative include p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like.

[0161] Examples of preferable antioxidant include sulfite, ascorbic acid and the like.

[0162] The compound of the present invention can prevent or treat diseases induced by promoted metabolism of cGMP, in human and other mammals, such as angina pectoris, heart failure, cardiac infarction, hypertension, pulmonary hypertension, arteriosclerosis, allergic diseases, asthma, renal diseases, cerebral function disorders, immunodeficiency, ophthalmic diseases, disorders of male or female genital function and the like, by inhibiting the action of cGMP-PDE, particularly cGMP-PDE V. While the dose of the compound of the present invention varies depending on the condition and body weight of administration subject, administration route and the like, the compound of the present invention as an active ingredient is generally given by intravenous, muscular injection and the like once to 3 times a day in a single dose of about 0.1-80 mg/kg body weight, preferably 1-25 mg/kg body weight, in the case of, for example, parenteral administration to an adult. In the case of oral or nasal administration, the dose is given at once or divided in three doses, wherein a single dose of the compound of the present invention as an active ingredient is about 1-100 mg/kg body weight, preferably 2-50 mg/kg body weight.

[0163] The present invention is explained in more detail by the following Reference Examples and Examples. These are mere examples and do not limit the present invention in any way.

[0164] The extraction by column chromatography in the following Reference Examples and Examples was performed under observation by TLC (thin-layer chromatography). In the TLC observation, $60F_{254}$ (Merck) was used as a TLC plate, the solvent used as an elution solvent in the column chromatography was used as a solvent and UV detector was used for detection. As silica gel for column, Kieselgel 60 (70-230 or 230-400 mesh) manufactured by Merck was used.

[0165] The NMR spectrum was measured with Varian Gemini 200 (200 MHz) type spectrometer using tetramethylsilane as an internal or external standard, and all δ values are shown in ppm. For mass analysis, cation was measured by atmospheric pressure chemical ionization (APCI) using platform II spectrometer (MICROMASS). The figures in parentheses for mixed solvents are mixing volume ratios of respective solvents and % of the mixed solvent means percent by volume. The abbreviations in Examples and Reference Examples mean the following.

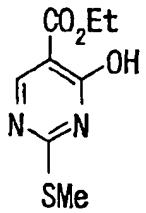
s : singlet
d : doublet
t : triplet
q : quartet
dd : double doublet
m : multiplet
br : broad
J : coupling constant

Examples

Reference Example 1

ethyl 2-methylthio-4-hydroxypyrimidine-5-carboxylate

[0166]



[0167] To a 4N sodium hydroxide solution (200 mL) was added S-methylisothioureasulfate (55.6 g, 0.2 mol), and after stirring for 30 min, at room temperature a solution of diethyl ethoxymethylenemalonate (80.8 mL, 0.35 mol) in ethanol (100 mL) was dropwise added slowly over 1 h. After stirring for 18 h, the precipitated crystals were collected by filtration, washed several times with cold ethanol and the obtained crystals were added to 1N hydrochloric acid (300 mL). The mixture was stirred for 30 min and the precipitated crystals were collected by filtration, washed several times with cold water and dried with heating under vacuum to give the title compound (26 g, 61%) as crystals.
^{1}H-NMR (δ ppm, $CDCl_3$): 1.42 (3H, t, J=7.0 Hz), 2.60 (3H, s) , 4.44 (2H, q, J=7.0 Hz), 8.76 (1H, s), 13.25 (1H, br)

Reference Example 2-1

ethyl 4-hydroxy-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

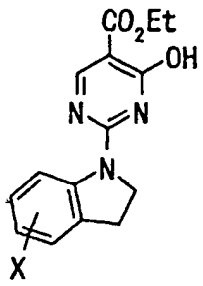
[0168] To a solution of indoline (3.58 g, 30 mmol) in ethanol (50 mL) was added ethyl 2-methylthio-4-hydroxypyrimidine-5-carboxylate (5.35 g, 25 mmol) and the mixture was heated under reflux for 18 h. The reaction mixture was allowed to cool to room temperature and the precipitated crystals were collected by filtration. The crystals were washed several times with cold ethanol and dried to give the title compound (5.5 g, 77%) as crystals.

[0169] In the same manner as in Reference Example 2-1, compounds of Reference Examples 2-2 to 2-14 were synthesized.

Reference Example 2-2: ethyl 2-(5-fluoro-2,3-dihydro-1H-indol-1-yl) -4-hydroxy-5-pyrimidinecarboxylate
Reference Example 2-3: ethyl 2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-hydroxy-5-pyrimidinecarboxylate
Reference Example 2-4: ethyl 4-hydroxy-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 2-5: ethyl 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-hydroxy-5-pyrimidinecarboxylate
Reference Example 2-6: ethyl 4-hydroxy-2-(6-nitro-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 2-7: ethyl 4-hydroxy-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 2-8: ethyl 4-hydroxy-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 2-9: ethyl (RS)-4-hydroxy-2-(3-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 2-10: ethyl 4-hydroxy-2-(7-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 2-11: ethyl (RS)-4-hydroxy-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 2-12: ethyl 4-hydroxy-2-(7-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 2-13: ethyl (R)-4-hydroxy-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 2-14: ethyl (S)-4-hydroxy-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

[0170] Respective structural formulas and NMR data are shown in the following Table.

[Table 1]



Reference Example No.	X	yield(%)	^{1}H-NMR(δ ppm, $CDCl_3$)
2-1	H	77	1.42 (3H, t, J=7.0 Hz), 3.21 (2H, t, J=7.6 Hz), 4.32 (2H, t, J=7.6 Hz), 4.42 (2H, q, J=7.2 Hz), 7.02 (1H, t, J=7.0 Hz), 7.20-7.30 (2H, m), 8.50 (1H, d, J=7.0 Hz), 8.84 (1H, s)
2-2	5-F	55	1.42 (3H, t, J=7.6 Hz), 3.19 (2H, t, J=8.4 Hz), 4.33 (2H, t, J=8.4 Hz), 4.42 (2H, q, J=7.0 Hz), 6.86-6.98 (2H, m), 8.39-8.50 (1H, br), 8.82 (1H, s)
2-3	5,6-OCH_2O	72	1.42 (3H, t, J=7.4 Hz), 3.10 (2H, t, J=8.8 Hz), 4.31 (2H, t, J=8.0 Hz), 4.41 (2H, q, J=7.4 Hz), 5.96 (2H, s), 6.70 (1H, s), 8.20 (1H, br s), 8.79 (1H, s)
2-4	5-MeO	82	1.42 (3H, t, J=7.6 Hz), 3.18 (2H, t, J=8.4 Hz), 3.81 (3H, s), 4.30 (2H, t, J=8.4 Hz), 4.41 (2H, q, J=7.6 Hz), 6.72-6.81 (2H, m), 8.40 (1H, d, J=7.5 Hz), 8.81 (1H, s)
2-5	5-Br	65	1.42 (3H, t, 7.6 Hz), 3.19 (2H, t, J=8.4 Hz), 4.32 (2H, t, J=8.4 Hz), 4.42 (2H, q, J=7.0 Hz), 7.30-7.38 (2H, m), 8.38 (1H, d, J=7.5 Hz), 8.83 (1H, s)
2-6	6-NO_2	45	1.44 (3H, t, J=7.0 Hz), 3.29 (2H, t, J=8.4 Hz), 4.37-4.50 (4H, m), 7.31 (1H, d, J=8.2 Hz), 7.90 (1H, dd, J=8.0, 2.2 Hz), 8.94 (1H, br s), 9.31 (1H, d, J=2.2 Hz)
2-7	4-MeO	78	1.42 (3H, t, J=7.0 Hz), 3.12 (2H, t, J=8.4 Hz), 3.86 (3H, s), 4.34 (2H, t, J=8.4 Hz), 4.42 (2H, q, J=7.0 Hz), 6.70 (1H, d, J=8.2 Hz), 7.18-7.28 (2H, m), 8.14 (1H, d, J=8.0 Hz), 8.83 (1H, s)
2-8	5-Me	76	1.42 (3H, t, J=7.4 Hz), 2.33 (3H, s), 3.17 (2H, t, J=8.8 Hz), 4.29 (2H, t, J=8.8 Hz), 4.42 (2H, q, J=6.8 Hz), 7.00-7.08 (2H, m), 8.36 (1H, d, J=8.8 Hz), 8.82 (1H, s)
2-9	(RS)-3-Me	84	1.32-1.47 (6H, m), 3.40-3.60 (1H, m), 3.84 (1H, dd, J=12.2, 6.6 Hz), 4.37-4.56 (4H, m), 7.05 (1H, t, J=7.2 Hz), 7.19-7.30 (2H, m), 8.46 (1H, br d, J=7.2 Hz), 8.84 (1H, s)

2-10	7-MeO	29	1.37 (3H, t, J=7.0 Hz), 3.13 (2H, t, J=8.2 Hz), 4.04 (3H, s), 4.34 (2H, q, J=7.0 Hz), 4.51 (2H, t, J=8.2 Hz), 6.89-7.00 (2H, m), 7.21 (1H, t, J=8.0 Hz), 8.66 (1H, s)
2-11	(RS)-2-Me	46	1.30-1.48 (6H, m), 2.70 (1H, d, 16.2 Hz), 3.42 (1H, dd, J=16.2, 9.2 Hz), 4.41 (2H, q, J=7.4 Hz), 4.98-5.13 (1H, m), 7.03 (1H, t, J=6.6 Hz), 7.20-7.30 (2H, m), 8.43 (1H, d, J=8.2 Hz), 8.82 (1H, s)
2-12	7-Me	41	1.41 (3H, t, J=7.4 Hz), 2.26 (3H, s), 3.06 (2H, t, J=8.2 Hz), 4.31-4.48 (4H, m), 6.95-7.20 (3H, m), 8.77 (2H, s)
2-13	(R)-2-Me	85	1.30-1.48 (6H, m), 2.70 (1H, d, 16.2 Hz), 3.42 (1H, dd, J=16.2, 9.2 Hz), 4.41 (2H, q, J=7.4 Hz), 4.98-5.13 (1H, m), 7.03 (1H, t, J=6.6 Hz), 7.20-7.30 (2H, m), 8.43 (1H, d, J=8.2 Hz), 8.82 (1H, s)
2-14	(S)-2-Me	57	1.30-1.48 (6H, m), 2.70 (1H, d, 16.2 Hz), 3.42 (1H, dd, J=16.2, 9.2 Hz), 4.41 (2H, q, J=7.4 Hz), 4.98-5.13 (1H, m), 7.03 (1H, t, J=6.6 Hz), 7.20-7.30 (2H, m), 8.43 (1H, d, J=8.2 Hz), 8.82 (1H, s)

Reference Example 3-1

ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxylate

[0171] To a solution of ethyl 4-hydroxy-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate (7.1 g, 27.6 mmol) in N,N-dimethylformamide (100 ml) were added potassium carbonate (7.8 g, 60 mmol) and 4-fluorobenzylbromide (3.74 ml, 30 mmol) and the mixture was stirred at 80°C for 18 h. The reaction mixture was allowed to cool to room temperature and water was added. The precipitated crystals were collected by filtration, washed several times with cold water and cold ether and dried to give the title compound (8.6 g, 79%).

[0172] In the same manner as in Reference Example 3-1, compounds of Reference Examples 3-2 to 3-22 were synthesized.

Reference Example 3-2: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-fluorobenzyl)oxy]-5-pyrimidinecarboxylate

Reference Example 3-3: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoromethyl)benzyl]oxy}-5-pyrimidinecarboxylate

Reference Example 3-4: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-5-pyrimidinecarboxylate

Reference Example 3-5: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-ethoxy-5-pyrimidinecarboxylate

Reference Example 3-6: ethyl 4-[(4-bromobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

Reference Example 3-7: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-(2-methoxyethoxy)-5-pyrimidinecarboxylate

Reference Example 3-8: ethyl 4-[(4-fluorobenzyl)oxy]-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

Reference Example 3-9: ethyl 2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-5-pyrimidinecarboxylate

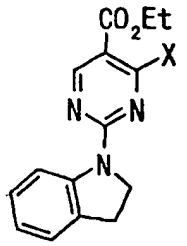
Reference Example 3-10: ethyl (RS)-4-[(4-fluorobenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

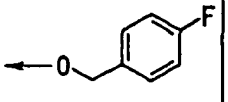
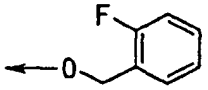
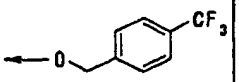
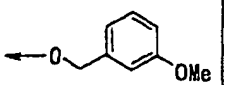
Reference Example 3-11: ethyl (RS)-4-[(3-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidine-

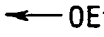
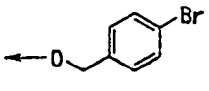
carboxylate
Reference Example 3-12: ethyl 2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxylate
Reference Example 3-13: ethyl 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxylate
Reference Example 3-14: ethyl 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-5-pyrimidinecarboxylate
Reference Example 3-15: ethyl 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-ethoxy-5-pyrimidinecarboxylate
Reference Example 3-16: ethyl 4-[(4-bromobenzyl)oxy]-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 3-17: ethyl 4-[(4-fluorobenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 3-18: ethyl 4-[(3-methoxybenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 3-19: ethyl 4-ethoxy-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 3-20: ethyl 4-[(4-bromobenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 3-21: ethyl 4-ethoxy-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 3-22: ethyl 4-[(4-bromobenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

[0173] Respective structural formulas and NMR data are shown in the following Tables.

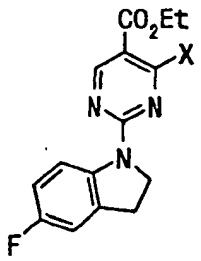
[Table 2]

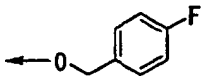
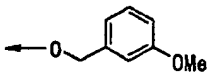


Reference Example No.	X	Yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
3-1		79	1.35 (3H, t, J=7.0 Hz), 3.22 (2H, t, J=8.4 Hz), 4.23-4.40 (4H, m), 5.56 (2H, s), 6.96-7.16 (3H, m), 7.17-7.28 (2H, m), 7.46-7.58 (2H, m), 8.20-8.50 (1H, br s), 8.93 (1H, s)
3-2		77	1.36 (3H, t, J=7.0 Hz), 3.21 (2H, t, J=8.4 Hz), 4.22-4.40 (4H, m), 5.67 (2H, s), 6.95-7.38 (6H, m), 7.66 (1H, t, J=6.6 Hz), 8.20-8.50 (1H, br), 8.94 (1H, s)
3-3		93	1.38 (3H, t, J=7.0 Hz), 3.21 (2H, t, J=8.4 Hz), 4.18-4.42 (4H, m), 5.64 (2H, s), 7.01 (1H, t, J=7.0 Hz), 7.18-7.29 (2H, m), 7.66 (4H, s), 8.10-8.50 (1H, br), 8.95 (1H, s)
3-4		82	1.35 (3H, t, J=7.0 Hz), 3.20 (2H, t, J=8.8 Hz), 3.82 (3H, s), 4.25-4.42 (4H, m), 5.54 (2H, s), 6.95-7.40 (6H, m), 7.35 (1H, t, J=8.6 Hz), 8.20-8.55 (1H, br), 8.91 (1H, s)

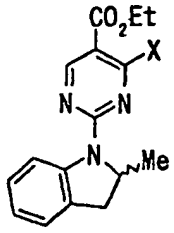
3-5		99	1.37 (3H, t, J=7.4 Hz), 1.52 (3H, t, J=7.0 Hz), 3.21 (2H, t, J=8.4 Hz), 4.23-4.38 (4H, m), 4.59 (2H, q, J=7.2 Hz), 7.00 (1H, t, J=6.6 Hz), 7.19-7.28 (2H, m), 8.32-8.42 (1H, br), 8.89 (1H, s)
3-6		94	1.37 (3H, t, J=7.0 Hz), 3.21 (2H, t, J=8.8 Hz), 4.21-4.40 (4H, m), 5.54 (2H, s), 7.01 (1H, t, J=7.0 Hz), 7.18-7.28 (2H, m), 7.41 (2H, d, J=8.0 Hz), 7.52 (2H, d, J=8.0 Hz), 8.17-8.50 (1H, br), 8.93 (1H, s)
3-7		98	1.37 (3H, t, J=7.0 Hz), 3.21 (2H, t, J=8.0 Hz), 3.49 (3H, s), 3.86 (2H, t, J=4.4 Hz), 4.22-4.40 (4H, m), 4.65 (2H, t, J=5.2 Hz), 7.00 (1H, t, J=7.2 Hz), 7.18-7.29 (2H, m), 8.23-8.42 (1H, br), 8.90 (1H, s)

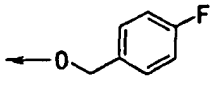
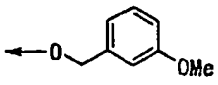
[Table 3]



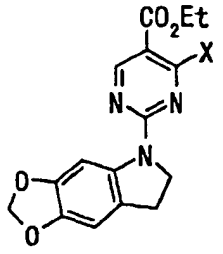
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
3-8		86	1.35 (3H, t, J=7.0 Hz), 3.20 (2H, t, J=8.8 Hz), 4.25-4.40 (4H, m), 5.53 (2H, s), 6.85-6.98 (2H, m), 7.08 (2H, t, J=8.8 Hz), 7.50 (2H, dd, J=5.4, 8.4 Hz), 8.15-8.43 (1H, br), 8.92 (1H, s)
3-9		81	1.36 (3H, t, J=7.0 Hz), 3.19 (2H, t, J=8.8 Hz), 3.82 (3H, s), 4.23-4.40 (4H, m), 5.56 (2H, s), 6.80-6.95 (3H, m), 7.07-7.12 (2H, m), 7.30 (1H, t, J=8.4 Hz), 8.00-8.42 (1H, br), 8.91 (1H, s)

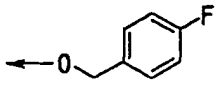
[Table 4]



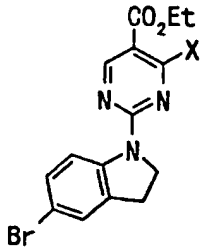
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
3-10		95	1.29-1.42 (6H, m), 2.62 (1H, d, J=16.0 Hz), 3.44 (1H, dd, J=9.2, 15.8 Hz), 4.33 (2H, q, J=9.4 Hz), 5.02 (1H, quintet, J=7.0 Hz), 5.54 (2H, s), 6.97-7.14 (3H, m), 7.19-7.28 (2H, m), 7.51 (2H, dd, J=5.4, 8.8 Hz), 8.29 (1H, d, J=7.0 Hz), 8.93 (1H, s)
3-11		99	1.30-1.44 (6H, m), 2.70 (1H, d, J=15.2 Hz), 3.43 (1H, dd, J=8.2, 15.2 Hz), 3.81 (3H, s), 4.34 (2H, q, J=7.0 Hz), 4.92-5.12 (1H, br), 5.56 (2H, s), 6.80-7.14 (4H, m), 7.18-7.35 (3H, m), 8.20-8.35 (1H, br), 8.92 (1H, s)

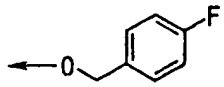
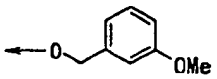
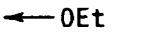
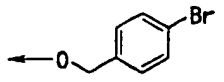
[Table 5]



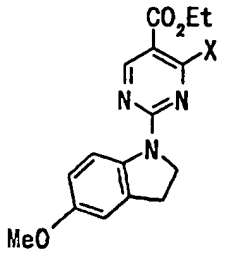
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
3-12		95	1.35 (3H, t, J=7.0 Hz), 3.11 (2H, t, J=8.4 Hz), 4.20-4.38 (4H, m), 5.53 (2H, s), 5.96 (2H, s), 6.71 (1H, s), 7.07 (2H, t, J=8.8 Hz), 7.44-7.53 (2H, m), 7.70-8.20 (1H, br), 8.89 (1H, s)

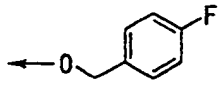
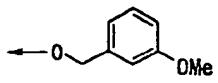
[Table 6]



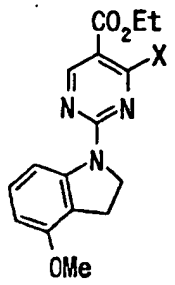
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
3-13		80	1.35 (3H, t, J=7.0 Hz), 3.20 (2H, t, J=8.8 Hz), 4.22-4.38 (4H, m), 5.53 (2H, s), 7.08 (2H, t, J=8.4 Hz), 7.29-7.39 (2H, m), 7.49 (2H, dd, J=5.6, 8.8 Hz), 8.08-8.30 (1H, br), 8.92 (1H, s)
3-14		83	1.36 (3H, t, J=7.0 Hz), 3.18 (2H, t, J=8.4 Hz), 3.82 (3H, s), 4.22-4.41 (4H, m), 5.55 (2H, s), 6.85 (1H, dd, J=3.0, 8.0 Hz), 7.05-7.12 (2H, m), 7.27-7.35 (3H, m), 8.00-8.30 (1H, br), 8.91 (1H, s)
3-15		94	1.37 (3H, t, J=7.0 Hz), 1.51 (3H, t, J=6.8 Hz), 3.19 (2H, t, J=8.6 Hz), 4.22-4.39 (4H, m), 4.55 (2H, q, J=7.0 Hz), 7.30-7.39 (2H, m), 8.17-8.33 (1H, br), 8.88 (1H, s)
3-16		73	1.37 (3H, t, J=7.2 Hz), 3.20 (2H, t, J=8.4 Hz), 4.22-4.40 (4H, m), 5.52 (2H, s), 7.29-7.43 (4H, m), 7.52 (2H, d, J=8.8 Hz), 8.00-8.30 (1H, br), 8.93 (1H, s)

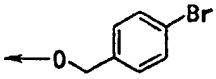
[Table 7]



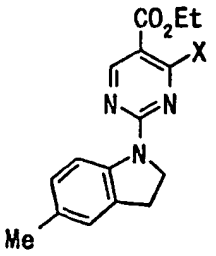
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
3-17		92	1.35 (3H, t, J=7.0 Hz), 3.19 (2H, t, J=8.4 Hz), 3.81 (3H, s), 4.20-4.38 (4H, m), 5.54 (2H, s), 6.71-6.82 (2H, m), 7.08 (2H, t, J=8.8 Hz), 7.43-7.53 (2H, m), 8.00-8.40 (1H, br), 8.90 (1H, s)
3-18		77	1.36 (3H, t, J=7.0 Hz), 3.18 (2H, t, J=8.4 Hz), 3.81 (6H, s), 4.15-4.41 (4H, m), 5.56 (2H, s), 6.68-6.88 (3H, m), 7.02-7.20 (2H, m), 7.20-7.38 (1H, m), 8.00-8.40 (1H, br), 8.90 (1H, s)

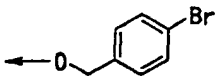
[Table 8]



Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
3-19	←OEt	87	1.37 (3H, t, J=7.4 Hz), 1.51 (3H, t, J=7.2 Hz), 3.12 (2H, t, J=8.8 Hz), 3.87 (3H, s), 4.25-4.40 (4H, m), 4.58 (2H, q, J=7.0 Hz), 6.58 (1H, d, J=8.0 Hz), 7.22 (1H, d, J=8.2 Hz), 8.00 (1H, br d, J=8.2 Hz), 8.88 (1H, s)
3-20		83	1.37 (3H, t, J=6.6 Hz), 3.12 (2H, t, J=9.2 Hz), 3.87 (3H, s), 4.23-4.40 (4H, m), 5.53 (2H, s), 6.59 (1H, d, J=8.4 Hz), 7.19 (1H, d, J=8.2 Hz), 7.41 (2H, d, J=8.4 Hz), 7.52 (2H, d, J=8.4 Hz), 7.80-8.05 (1H, br), 8.92 (1H, s)

[Table 9]



Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
3-21	←OEt	81	1.36 (3H, t, J=6.8 Hz), 1.51 (3H, t, J=7.2 Hz), 2.33 (3H, s), 3.17 (2H, t, J=8.4 Hz), 4.20-4.38 (4H, m), 4.57 (2H, q, J=7.2 Hz), 7.00-7.08 (2H, m), 8.14-8.30 (1H, br), 8.88 (1H, s)
3-22		89	1.36 (3H, t, J=7.0 Hz), 2.33 (3H, s), 3.17 (2H, t, J=8.6 Hz), 4.20-4.40 (4H, m), 5.53 (2H, s), 6.99-7.08 (2H, m), 7.41 (2H, d, J=8.4 Hz), 7.52 (2H, d, J=8.4 Hz), 8.00-8.35 (1H, br), 8.92 (1H, s)

Reference Example 4-1

Ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate

[0174] To a solution of ethyl 4-hydroxy-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate (500 mg, 1.75 mmol) in N,N-dimethylformamide (10 mL) were added potassium carbonate (500 g, 4 mmol), sodium iodide (300 mg, 2 mmol) and 4-methoxybenzyl chloride (0.29 mL, 2 mmol), and the mixture was stirred at 80°C for 18 h. The reaction mixture was allowed to cool to room temperature and water was added. The precipitated crystals were collected by filtration, washed several times with cold water and cold ether, and dried to give the title compound (550 mg, 78%).

[0175] In the same manner as in Reference Example 4-1, compounds of Reference Examples 4-2 to 4-32 were synthesized.

Reference Example 4-2: ethyl 4-[(2,6-difluorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 4-3: ethyl 4-[(4-chlorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 4-4: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3,4-dimethylbenzyl)oxy]-5-pyrimidinecarboxylate
Reference Example 4-5: ethyl 4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate
Reference Example 4-6: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-5-pyrimidinecarboxylate
Reference Example 4-7: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-isopropoxybenzyl)oxy]-5-pyrimidinecarboxylate
Reference Example 4-8: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-ethoxybenzyl)oxy]-5-pyrimidinecarboxylate
Reference Example 4-9: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate

Reference Example 4-10: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxy-3-methylbenzyl)oxy]-5-pyrimidinecarboxylate

Reference Example 4-11: ethyl 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

Reference Example 4-12: ethyl 4-(2,3-dihydro-1-benzofuran-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

Reference Example 4-13: ethyl 4- (1,3-benzodioxol-5-ylmethoxy)-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

Reference Example 4-14: ethyl 2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate Reference Example 4-15: ethyl 2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate

Reference Example 4-16: ethyl 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate Reference Example 4-17: ethyl 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-5-pyrimidinecarboxylate Reference Example 4-18: ethyl 4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate Reference Example 4-19: ethyl 4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate Reference Example 4-20: ethyl 4-[(4-methoxybenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate Reference Example 4-21: ethyl 4-[(2,5-dimethoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate Reference Example 4-22: ethyl 4-[(4-methoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate Reference Example 4-23: ethyl 4-[(4-methoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate Reference Example 4-24: ethyl 4-[(2,5-dimethoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate Reference Example 4-25: ethyl (RS)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate Reference Example 4-26: ethyl (RS)-4-[(4-methoxybenzyl)oxy]-2-(3-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate Reference Example 4-27: ethyl 4-[(4-methoxybenzyl)oxy]-2-(7-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate Reference Example 4-28: ethyl (R)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate Reference Example 4-29: ethyl (R)-4-[(3-fluoro-4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

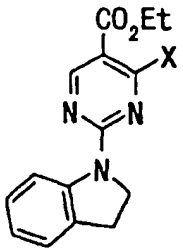
Reference Example 4-30: ethyl (R)-4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

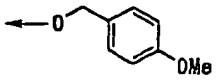
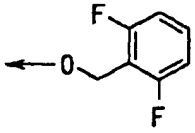
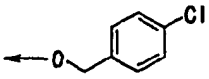
Reference Example 4-31: ethyl (R)-4-[(2-fluoro-4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

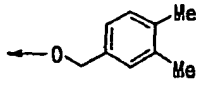
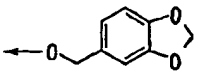
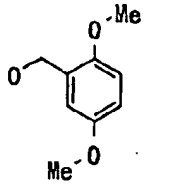
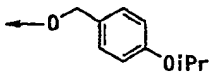
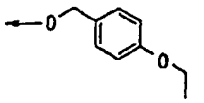
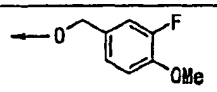
Reference Example 4-32: ethyl (R)-4-[(2-chloro-4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

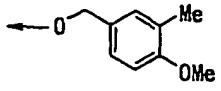
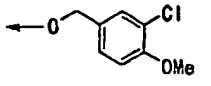
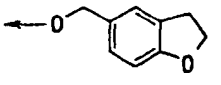
Reference Example 4-33: ethyl (S)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

[Table 10]

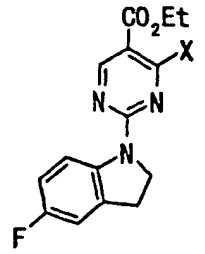


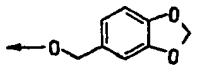
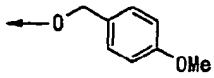
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-1		78	1.34(3H, t, J=7.0 Hz0, 3.22 (2H, t, J=8.4 Hz), 3.81 (3H, s), 4.32 (2H, q, J=6.8 Hz), 5.53 (2H, s), 6.88-7.08 (3H, m), 7.18-7.30 (2H, m), 7.45 (2H, d, J=8.8 Hz), 8.38 (1H, br d, J=8.0 Hz), 8.92 (1H, s)
4-2		92	1.24 (3H, t, J=7.0 Hz), 3.23 (2H, t, J=8.8 Hz), 4.19-4.20 (2H, m), 5.65 (2H, s), 6.88-7.06 (3H, m), 7.20-7.42 (3H, m), 8.42 (1H, d, J=7.4 Hz), 8.91 (1H, s)
4-3		91	1.36 (3H, t, J=7.0 Hz), 3.21 (2H, t, J=8.6 Hz), 4.20-4.40 (2H, m), 5.56 (2H, s), 7.01 (1H, t, J=7.4 Hz), 7.18-7.28 (2H, m), 7.36 (2H, d, J=8.4 Hz), 7.48 (2H, d, J=8.4 Hz), 8.20-8.50 (1H, br), 8.93 (1H, s)

4-4		73	1.36 (3H, t, J=7.4 Hz), 2.26 (3H, s), 2.34 (3H, s), 3.22 (2H, t, J=8.4 Hz), 4.24-4.40 (4H, m), 5.54 (2H, s), 7.01 (1H, t, J=8.0 Hz), 7.08-7.30 (4H, m), 8.29-8.45 (1H, br), 8.92 (1H, s)
4-5		98	1.36 (3H, t, J=7.4 Hz), 3.22 (2H, t, J=8.0 Hz), 4.25-4.38 (4H, m), 5.50 (2H, s), 5.96 (2H, s), 6.81 (1H, d, J=8.0 Hz), 6.93-7.04 (3H, m), 7.19-7.28 (2H, m), 8.24-8.45 (1H, br), 8.92 (1H, s)
4-6		80	1.37 (3H, t, J=6.8 Hz), 3.20 (2H, t, J=9.2 Hz), 3.77 (3H, s), 3.86 (3H, s), 4.24-4.41 (4H, m), 5.62 (2H, s), 6.78-6.86 (2H, m), 6.99 (1H, t, J=7.4 Hz), 7.17-7.29 (3H, m), 8.20-8.40 (1H, br), 8.93 (1H, s)
4-7		61	1.25 (6H, d, J=6.0 Hz), 3.19 (2H, t, J=8.0 Hz), 4.26 (2H, t, J=8.6 Hz), 4.61 (1H, sevenplet, J=6.0 Hz), 5.50 (2H, s), 6.92 (2H, d, J=8.8 Hz), 7.02 (1H, d, J=7.6 Hz), 7.18-7.32 (2H, m), 7.42 (2H, d, J=8.6 Hz), 8.31 (1H, br s), 8.80 (1H, s)
4-8		74	1.34 (3H, t, J=7.4 Hz), 1.41 (3H, t, J=7.0 Hz), 3.21 (2H, t, J=8.4 Hz), 4.03 (2H, q, J=7.0 Hz), 4.25-4.39 (4H, m), 5.53 (2H, s), 6.90 (2H, d, J=9.4 Hz), 7.00 (1H, t, J=6.6 Hz), 7.18-7.30 (2H, m), 7.44 (2H, d, J=8.8 Hz), 8.36 (1H, br d, J=9.2 Hz), 8.91 (1H, s)
4-9		81	1.36 (3H, t, J=7.4 Hz), 3.22 (2H, t, J=8.8 Hz), 3.90 (3H, s), 4.24-4.40 (4H, m), 5.51 (2H, s), 6.90-7.07 (2H, m), 7.20-7.32 (4H, m), 8.35 (1H, br s), 8.93 (1H, s)

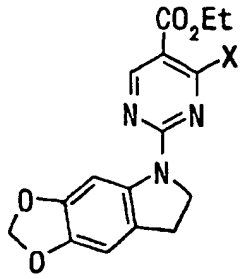
4-10		80	1.34 (3H, t, J=7.2 Hz), 2.23 (2H, t, J=8.8 Hz), 3.22 (2H, t, J=8.8 Hz), 3.83 (3H, s), 4.25-4.39 (4H, m), 5.51 (2H, s), 6.82 (1H, d, J=8.0 Hz), 7.00 (1H, t, J=7.0 Hz), 7.00-7.38 (4H, m), 8.40 (1H, br s), 8.91 (1H, s)
4-11		81	1.37 (3H, t, J=7.0 Hz), 3.22 (2H, t, J=8.8 Hz), 3.91 (3H, s), 4.25-4.40 (4H, m), 5.50 (2H, s), 6.90-7.08 (2H, m), 7.20-7.30 (2H, m), 7.41 (1H, dd, J=2.2, 8.4 Hz), 7.56 (1H, d, J=2.2 Hz), 8.20-8.45 (1H, br), 8.93 (1H, s)
4-12		60	1.34 (3H, t, J=7.0 Hz), 3.22 (4H, t, J=8.8 Hz), 4.26-4.39 (4H, m), 4.58 (2H, t, J=8.8 Hz), 5.52 (2H, s), 6.78 (1H, d, J=8.2 Hz), 7.01 (1H, t, J=7.8 Hz), 7.20-7.31 (3H, m), 7.38 (1H, s), 8.37 (1H, br s), 8.92 (1H, s)

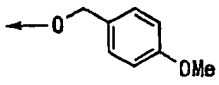
[Table 11]



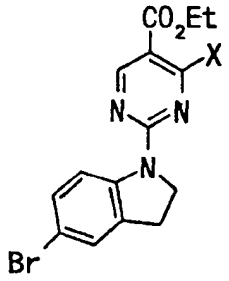
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-13		86	1.36 (3H, t, J=7.4 Hz), 3.20 (2H, t, J=8.0 Hz), 4.27-4.39 (4H, m), 5.48 (2H, s), 5.97 (2H, s), 6.79-7.04 (5H, m), 8.10-8.43 (1H, br), 8.90 (1H, s)
4-14		92	1.34 (3H, t, J=8.0 Hz), 3.21 (2H, t, J=8.4 Hz), 3.81 (3H, s), 4.24-4.38 (4H, m), 5.51 (2H, s), 6.84-6.96 (4H, m), 7.44 (2H, d, J=8.8 Hz), 8.17-8.43 (1H, br), 8.90 (1H, s)

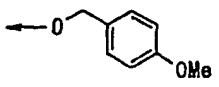
[Table 12]

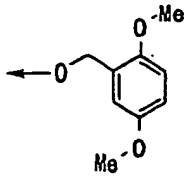
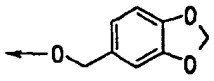


Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-15		100	1.34 (3H, t, J=7.4 Hz), 3.12 (2H, t, J=8.4 Hz), 3.81 (3H, s), 4.24-4.37 (4H, m), 5.50 (2H, s), 5.96 (2H, s), 6.71 (1H, s), 6.91 (2H, d, J=8.8 Hz), 7.45 (2H, d, J=8.8 Hz), 7.90-8.25 (1H, br), 8.87 (1H, s)

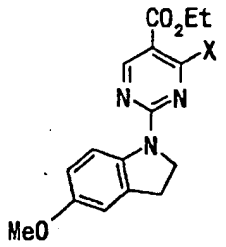
[Table 13]

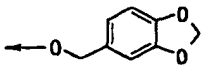
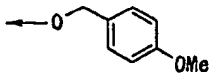


Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-16		81	1.34 (3H, t, J=7.0 Hz), 3.20 (2H, t, J=8.4 Hz), 3.81 (3H, s), 4.24-4.38 (4H, m), 5.51 (2H, s), 6.91 (2H, d, J=8.6 Hz), 7.29-7.36 (2H, m), 7.44 (2H, d, J=8.6 Hz), 8.16-8.32 (1H, br), 8.90 (1H, s)

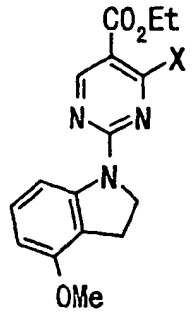
4-17		81	1.37 (3H, t, J=7.0 Hz), 3.18 (2H, t, J=8.4 Hz), 3.77 (3H, s), 3.86 (3H, s), 4.23-4.41 (4H, m), 5.59 (2H, s), 6.79-6.85 (2H, m), 7.21-7.33 (3H, m), 8.05-8.30 (1H, br), 8.92 (1H, s)
4-18		78	1.40 (3H, t, J=7.4 Hz), 3.20 (2H, t, J=8.8 Hz), 4.23-4.39 (4H, m), 5.47 (2H, s), 5.97 (2H, s), 6.81 (1H, d, J=7.8 Hz), 6.90-7.05 (2H, m), 7.28-7.38 (2H, m), 8.10-8.35 (1H, br), 8.91 (1H, s)

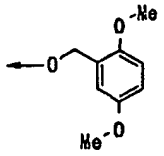
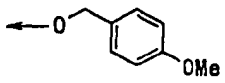
[Table 14]



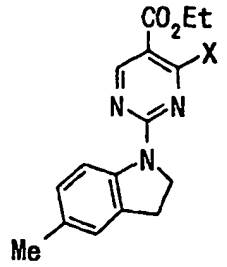
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-19		84	1.35 (3H, t, J=7.0 Hz), 3.19 (2H, t, J=8.6 Hz), 3.81 (3H, s), 4.22-4.37 (4H, m), 5.48 (2H, br s), 5.96 (2H, s), 6.72-6.84 (3H, m), 6.95-7.05 (2H, m), 8.00-8.23 (1H, br), 8.90 (1H, s)
4-20		63	1.34 (3H, t, J=J=7.0 Hz), 3.19 (2H, t, J=8.0 Hz), 3.81 (6H, s), 4.25-4.36 (4H, m), 5.52 (2H, s), 6.72-6.83 (2H, m), 6.91 (2H, d, J=8.8 Hz), 7.46 (2H, d, J=8.8 Hz), 8.10-8.45 (1H, br), 8.89 (1H, s)

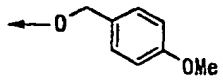
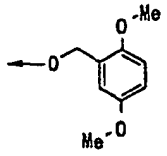
[Table 15]



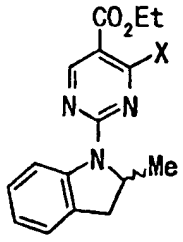
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-21		84	1.37 (3H, t, J=7.0 Hz), 3.11 (2H, t, J=8.8 Hz), 3.77 (3H, s), 3.85 (6H, s), 4.24-4.40 (4H, m), 5.61 (2H, s), 6.57 (2H, d, J=8.0 Hz), 6.80-6.83 (2H, m), 7.13-7.24 (2H, m), 7.90-8.05 (1H, br), 8.92 (1H, s)
4-22		84	1.34 (3H, t, J=7.4 Hz), 3.13 (2H, t, J=8.4 Hz), 3.81 (3H, s), 3.87 (3H, s), 4.25-4.37 (4H, m), 5.53 (2H, s), 6.59 (1H, d, J=8.4 Hz), 6.91 (2H, d, J=8.8 Hz), 7.22 (1H, t, J=8.2 Hz), 7.45 (2H, d, J=8.8 Hz), 7.95-8.09 (1H, br), 8.90 (1H, s)

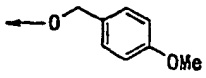
[Table 16]



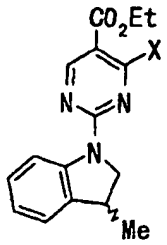
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-23		86	1.34 (3H, t, J=7.4 Hz), 2.33 (3H, s), 3.17 (2H, t, J=8.4 Hz), 3.81 (3H, s), 4.23-4.38 (4H, m), 5.53 (2H, s), 6.91 (2H, d, J=8.8 Hz), 6.99-7.08 (2H, m), 7.45 (2H, d, J=8.8 Hz), 8.15-8.29 (1H, br), 8.90 (1H, s)
4-24		90	1.37 (3H, t, J=7.0 Hz), 2.33 (3H, s), 3.16 (2H, t, J=8.4 Hz), 3.77 (3H, s), 3.86 (3H, s), 4.20-4.40 (4H, m), 5.61 (2H, s), 6.80-6.85 (2H, m), 6.96-7.06 (3H, m), 8.00-8.40 (1H, br), 8.92 (1H, s)

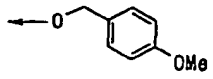
[Table 17]



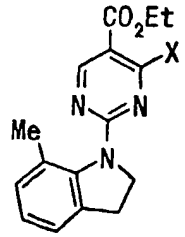
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-25		100	1.36 (3H, d, J=7.0 Hz), 2.71 (1H, d, J=16.8 Hz), 3.44 (1H, dd, J=7.0, 15.6 Hz), 3.82 (3H, s), 4.32 (2H, q, J=7.0 Hz), 4.95-5.09 (1H, m), 5.52 (2H, s), 6.92 (2H, d, J=8.8 Hz), 7.02 (1H, t, J=8.0 Hz), 7.20-7.30 (2H, m), 7.45 (2H, d, J=8.4 Hz), 8.31 (1H, d, J=8.4 Hz), 8.91 (1H, s)

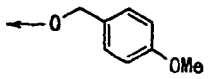
[Table 18]



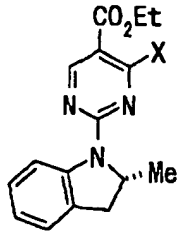
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-26		72	1.34 (3H, t, J=7.2 Hz), 3.43-3.58 (1H, m), 3.73-3.88 (4H, m), 4.32 (2H, q, J=7.0 Hz), 4.50 (1H, dd, J=9.8, 12.0 Hz), 5.54 (2H, s), 6.92 (2H, d, J=8.8 Hz), 7.04 (1H, t, J=6.6 Hz), 7.19-7.28 (2H, m), 7.46 (2H, d, J=8.4 Hz), 8.28-8.39 (1H, br), 8.91 (1H, s)

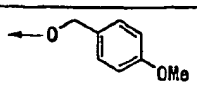
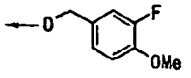
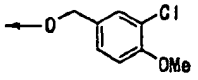
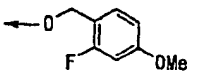
[Table 19]

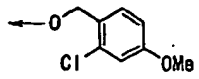


Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-27		46	1.33 (3H, t, J=7.0 Hz), 2.25 (3H, s), 3.05 (2H, t, J=7.4 Hz), 3.80 (3H, s), 4.30 (2H, q, J=6.8 Hz), 4.43 (2H, t, J=7.8 Hz), 5.42 (2H, s), 6.85 (2H, d, J=8.8 Hz), 7.00-7.15 (3H, m), 7.35 (2H, d, J=8.8 Hz), 8.83 (1H, s)

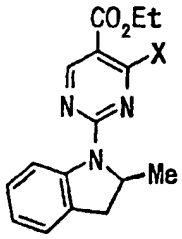
[Table 20]

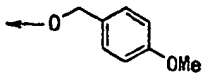


Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-28		96	1.36 (3H, d, J=7.0 Hz), 2.71 (1H, d, J=16.8 Hz), 3.44 (1H, dd, J=7.0, 15.6 Hz), 3.82 (3H, s), 4.32 (2H, q, J=7.0 Hz), 4.95-5.09 (1H, m), 5.52 (2H, s), 6.92 (2H, d, J=8.8 Hz), 7.02 (1H, t, J=8.0 Hz), 7.20-7.30 (2H, m), 7.45 (2H, d, J=8.4 Hz), 8.31 (1H, d, J=8.4 Hz), 8.91 (1H, s)
4-29		97	1.30-1.40 (6H, m), 2.72 (1H, d, J=16.4 Hz), 3.44 (1H, dd, J=9.2, 15.4 Hz), 3.90 (3H, s), 4.34 (2H, q, J=7.4 Hz), 4.95-5.13 (1H, m), 5.50 (2H, s), 6.90-7.15 (2H, m), 7.20-7.32 (4H, m), 8.28 (1H, d, J=9.2 Hz), 8.92 (1H, s)
4-30		94	1.30-1.42 (6H, m), 2.72 (1H, d, J=15.8 Hz), 3.43 (1H, dd, J=9.4, 14.0 Hz), 3.91 (3H, s), 4.34 (2H, q, J=7.0 Hz), 4.95-5.08 (1H, m), 5.49 (2H, s), 6.88-7.08 (2H, m), 7.20-7.35 (1H, m), 7.37-7.44 (2H, m), 7.55 91H, d, J=2.2 Hz), 8.29 (1H, d, J=7.0 Hz), 8.92 (1H, s)
4-31		98	1.28-1.40 (6H, m), 2.72 (1H, d, J=16.6 Hz), 3.44 (1H, dd, J=9.6, 15.8 Hz), 3.80 (3H, s), 4.32 (2H, q, J=7.0 Hz), 4.95-5.12 (1H, m), 5.57 (2H, s), 6.62-6.77 (2H, m), 7.02 (1H, t, J=7.4 Hz), 7.20-7.35 (2H, m), 7.52 (1H, t, J=8.4 Hz), 8.32 (1H, d, J=8.6 Hz), 8.92 (1H, s)

4-32		100	1.30-1.41 (6H, m), 2.72 (1H, d, J=16.4 Hz), 3.44 (1H, dd, J=9.6, 16.2 Hz), 3.81 (3H, s), 4.35 (2H, q, J=7.4 Hz), 4.95-5.10 (1H, m), 5.62 (2H, s), 6.85 (1H, dd, J=2.2, 8.4 Hz), 6.97 (1H, d, J=2.4 Hz), 7.04 (1H, d, J=6.8 Hz), 7.19-7.28 (2H, m), 7.62 (1H, d, J=8.8 Hz), 8.29 (1H, d, J=7.0 Hz), 8.93 (1H, s)

[Table 21]



Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
4-33		66	1.36 (3H, d, J=7.0 Hz), 2.71 (1H, d, J=16.8 Hz), 3.44 (1H, dd, J=7.0, 15.6 Hz), 3.82 (3H, s), 4.32 (2H, q, J=7.0 Hz), 4.95-5.09 (1H, m), 5.52 (2H, s), 6.92 (2H, d, J=8.8 Hz), 7.02 (1H, t, J=8.0 Hz), 7.20-7.30 (2H, m), 7.45 (2H, d, J=8.4 Hz), 8.31 (1H, d, J=8.4 Hz), 8.91 (1H, s)

Reference Example 5-1

ethyl 4-chloro-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

[0176] To ethyl 4-hydroxy-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate (2.85 g, 10 mmol) was added phos-

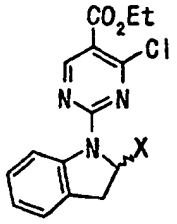
phorus oxychloride (10 mL, 2 mmol) and the mixture was stirred at 120°C for 15 h. The reaction mixture was concentrated under reduced pressure. The obtained residue was dissolved in ethyl acetate, washed with saturated aqueous sodium hydrogencarbonate solution (×3) and saturated brine (×1) and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure to give the title compound (2.9 g, 100%).

[0177] In the same manner as in Reference Example 5-1, a compound of Reference Example 5-2 was synthesized.

Reference Example 5-2: (RS)-ethyl 4-chloro-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

[0178] Respective structural formulas and NMR data are shown in the following Table.

[Table 22]

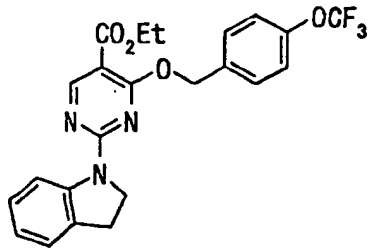


Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
5-1	H	100	1.42 (3H, t, J=7.2 Hz), 3.21 (2H, t, J=7.6 Hz), 4.31 (2H, t, J=7.6 Hz), 4.42 (2H, q, J=7.2 Hz), 7.03 (1H, t, J=7.2 Hz), 7.20-7.30 (2H, m), 8.50 (1H, d, J=7.6 Hz), 8.84 (1H, s)
5-2	Me	100	1.34-1.43 (6H, m), 2.74 (1H, d, J=15.8 Hz), 3.45 (1H, dd, J=9.0, 15.6 Hz), 4.38 (2H, q, J=7.4 Hz), 4.97-5.13 (1H, m), 7.07 (1H, t, J=7.2 Hz), 7.22-7.32 (2H, m), 8.36 (1H, d, J=8.2 Hz), 8.98 (1H, s)

Reference Example 6

ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoromethoxy)benzyl]oxy}-5-pyrimidinecarboxylate

[0179]



[0180] To a solution of ethyl 4-chloro-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate (520 mg, 1.72 mmol) in N,N-dimethylformamide (5 mL) was added potassium carbonate (829 mg, 6 mmol) and 4-(trifluoro)methoxybenzyl alcohol (384 mg, 2 mmol) and the mixture was stirred at 100°C for 18 h. The reaction mixture was allowed to cool to room temperature and water was added, which was followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure and the residue was applied to silica gel column chromatography and eluted with hexane-ethyl acetate (4:1) to give the title compound (420 mg, 53%).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.36 (3H, t, J=7.0 Hz), 3.22 (2H, t, J=8.8 Hz), 4.20-4.40 (4H, m), 5.59 (2H, s), 7.01 (1H, t, J=7.8 Hz), 7.18-7.28 (3H, m), 7.57 (2H, d, J=8.8 Hz), 8.20-8.40 (1H, br), 8.94 (1H, s)

Reference Example 7-1

ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)amino]-5-pyrimidinecarboxylate

[0181] To a solution of ethyl 4-chloro-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate (607 mg, 2.0 mmol) in isopropanol (5 mL) were added sodium carbonate (424 mg, 4 mmol) and 4-fluorobenzylamine (313 mg, 4 mmol) and the mixture was heated under reflux for 18 h. The reaction mixture was allowed to cool to room temperature and water was added. The precipitated crystals were collected by filtration, washed several times with cold water and cold ether and dried to give the title compound (637 mg, 81%).

[0182] In the same manner as in Reference Example 7-1, compounds of Reference Examples 7-2 to 7-16 were synthesized.

Reference Example 7-2: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoro)benzyl]amino)-5-pyrimidinecarboxylate

Reference Example 7-3: ethyl 4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

Reference Example 7-4: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-phenylpropyl)amino]-5-pyrimidinecarboxylate

Reference Example 7-5: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxyphenethyl)amino]-5-pyrimidinecarboxylate

Reference Example 7-6: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-thienylmethyl)amino]-5-pyrimidinecarboxylate

Reference Example 7-7: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-furylmethyl)amino]-5-pyrimidinecarboxylate

Reference Example 7-8: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluorobenzyl)amino]-5-pyrimidinecarboxylate

Reference Example 7-9: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)amino]-5-pyrimidinecarboxylate

Reference Example 7-10: ethyl 4-[(2,6-difluorobenzyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

Reference Example 7-11: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3,4-dimethoxybenzyl)amino]-5-pyrimidinecarboxylate

Reference Example 7-12: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methylbenzyl)amino]-5-pyrimidinecarboxylate

Reference Example 7-13: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-pyridinylmethyl)amino]-5-pyrimidinecarboxylate

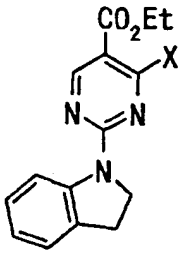
Reference Example 7-14: ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-pyridinylmethyl)amino]-5-pyrimidinecarboxylate

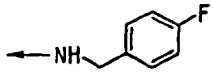
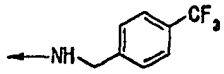
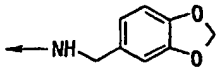
Reference Example 7-15: ethyl (RS)-4-[(4-methoxybenzyl)amino]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate

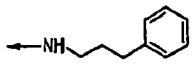
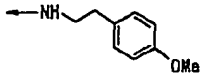
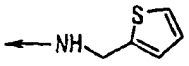
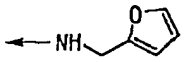
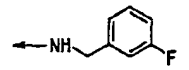
Reference Example 7-16: ethyl (RS)-4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl) -5-pyrimidinecarboxylate

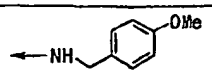
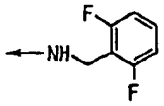
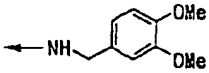
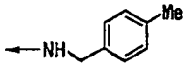
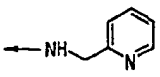
[0183] Respective structural formulas and NMR data are shown in the following Table.

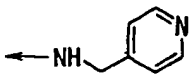
[Table 23]



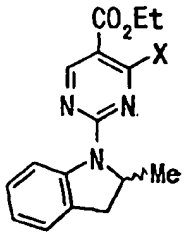
Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
7-1		81	1.37 (3H, t, J=7.0 Hz), 3.17 (2H, d, J=8.0 Hz), 4.20-4.35 (4H, m), 4.75 (2H, d, J=5.6 Hz), 6.90-7.24 (5H, m), 7.35 (2H, dd, J=4.0, 7.0 Hz), 8.21-8.33 (1H, br), 8.51-8.62 (1H, br), 8.78 (1H, s)
7-2		99	1.38 (3H, t, J=7.2 Hz), 3.14 (2H, t, J=8.4 Hz), 4.13-4.36 (4H, m), 4.85 (2H, d, J=6.0 Hz), 6.93 (1H, t, J=8.0 Hz), 7.00-7.14 (1H, br), 7.18 (1H, d, J=8.0 Hz), 7.49 (2H, d, J=8.0 Hz), 7.60 (2H, d, J=8.0 Hz), 8.00-8.35 (1H, br), 8.68 (1H, br s), 8.79 (1H, s)
7-3		85	1.36 (3H, t, J=7.2 Hz), 3.17 (2H, t, J=8.4 Hz), 4.20-4.35 (4H, m), 4.69 (2H, d, J=5.4 Hz), 5.94 (2H, s), 6.74-6.98 (4H, m), 7.10-7.24 (2H, m), 7.32 (1H, d, J=8.8 Hz), 8.51 (1H, br s), 8.77 (1H, s)

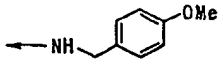
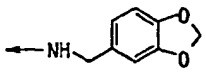
7-4		100	1.37 (3H, t, J=7.0 Hz), 2.04 (2H, quintet, J=7.6 Hz), 2.76 (2H, t, J=8.0 Hz), 3.16 (2H, t, J=8.8 Hz), 3.59 (2H, q, J=6.2 Hz), 4.16-4.36 (4H, m), 6.96 (1H, t, J=7.4 Hz), 7.12-7.32 (7H, m), 8.25 (1H, br s), 8.40 (1H, d, J=8.4 Hz), 8.74 (1H, s)
7-5		91	1.35 (3H, t, J=7.0 Hz), 2.94 (2H, t, J=6.8 Hz), 3.19 (2H, t, J=8.4 Hz), 3.69-3.83 (5H, m), 4.23-4.34 (4H, m), 6.87 (2H, d, J=8.4 Hz), 6.96 (1H, t, J=7.2 Hz), 7.14-7.25 (4H, m), 8.28 (1H, br s), 8.45 (1H, d, J=8.0 Hz), 8.74 (1H, s)
7-6		100	1.36 (3H, t, J=7.4 Hz), 3.18 (2H, t, J=8.4 Hz), 4.23-4.34 (4H, m), 4.95 (2H, d, J=5.2 Hz), 6.91-7.08 (3H, m), 7.13-7.23 (2H, m), 8.39 (1H, d, J=8.2 Hz), 8.48-8.62 (1H, br), 8.77 (1H, s)
7-7		92	1.36 (3H, t, J=6.8 Hz), 3.15 (2H, t, J=8.4 Hz), 4.22-4.35 (4H, m), 4.77 (2H, d, J=5.2 Hz), 6.25-6.34 (2H, m), 6.96 (1H, t, J=8.0 Hz), 7.16-7.25 (2H, m), 7.39 (1H, s), 8.39 (1H, d, J=8.2 Hz), 8.40-8.55 (1H, br s), 8.76 (1H, s)
7-8		92	1.38 (3H, t, J=6.8 Hz), 3.15 (2H, t, J=8.4 Hz), 4.18-4.37 (4H, m), 4.78 (2H, d, J=5.8 Hz), 6.88-7.02 (2H, m), 7.04-7.23 (3H, m), 7.24-7.36 (1H, m), 8.10-8.33 (1H, br), 8.62 (1H, br s), 8.79 (1H, s)

7-9		95	1.36 (3H, t, J=7.0 Hz), 3.17 (2H, t, J=8.4 Hz), 3.80 (3H, s), 4.22-4.34 (4H, m), 4.72 (2H, d, J=5.6 Hz), 6.84-6.98 (3H, m), 7.09-7.21 (2H, m), 7.31 (2H, d, J=9.4 Hz), 8.33 (1H, d, J=8.0 Hz), 8.50 (1H, br s), 8.77 (1H, s)
7-10		100	1.35 (3H, t, J=7.0 Hz), 3.19 (2H, t, J=8.4 Hz), 4.21-4.37 (4H, m), 4.90 (2H, d, J=5.2 Hz), 6.85-7.00 (3H, m), 7.16-7.29 (3H, m), 8.42-8.57 (2H, m), 8.76 (1H, s)
7-11		100	1.36 (3H, t, J=7.4 Hz), 3.16 (2H, t, J=8.4 Hz), 3.85 (3H, s), 3.87 (3H, s), 4.22-4.34 (4H, m), 4.72 (2H, d, J=5.4 Hz), 6.80-6.98 (4H, m), 7.09-7.22 (2H, m), 8.34 (1H, d, J=8.0 Hz), 8.50 (1H, br s), 8.77 (1H, s)
7-12		100	1.36 (3H, t, J=7.4 Hz), 2.33 (3H, s), 3.16 (2H, t, J=8.4 Hz), 4.20-4.35 (4H, m), 4.75 (2H, d, J=5.6 Hz), 6.93 (1H, t, J=8.0 Hz), 7.09-7.31 (5H, m), 8.31 (1H, d, J=8.0 Hz), 8.53 (1H, br s), 8.77 (1H, s)
7-13		86	1.39 (3H, t, J=7.0 Hz), 3.14 (2H, t, J=8.6 Hz), 4.22 (2H, t, J=8.8 Hz), 4.34 (2H, q, J=7.2 Hz), 4.92 (2H, d, J=5.6 Hz), 6.92 (1H, t, J=8.4 Hz), 7.08-7.23 (3H, m), 7.33 (1H, d, J=7.6 Hz), 7.64 (1H, dt, J=1.8, 7.6 Hz), 8.17-8.31 (1H, br), 8.63 (1H, d, J=4.8 Hz), 8.79 (1H, s), 8.94 (1H, br t, J=5.0 Hz)

7-14		72	1.39 (3H, t, J=6.8 Hz), 3.13 (2H, t, J=8.6 Hz), 4.00-4.40 (4H, m), 4.80 (2H, d, J=5.8 Hz), 6.92 (1H, t, J=8.2 Hz), 6.97-6.12 (1H, br), 7.18 (1H, d, J=8.0 Hz), 7.29 (2H, d, J=6.2 Hz), 7.90-8.30 (1H, br), 8.55 (2H, d, J=4.6 Hz), 8.62-8.74 (1H, br), 8.80 (1H, s)

[Table 24]



Reference Example No.	X	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
7-15		83	1.29-1.40 (6H, m), 2.66 (1H, d, J=15.8 Hz0, 3.39 (1H, dd, J=9.4, 16.0 Hz), 3.80 (3H, s), 4.28 (2H, q, J=7.2 Hz), 4.70 (2H, d, J=5.6 Hz), 4.90-5.08 (1H, m), 6.82-7.00 (3H, m), 7.10-7.32 (3H, m), 8.27 (1H, d, J=7.8 Hz), 8.40 (1H, br t, J=7.0 Hz), 8.76 (1H, s)
7-16		90	1.28-1.40 (6H, m), 2.66 (1H, d, J=16.4 Hz), 3.39 (1H, dd, J=9.4, 15.6 Hz), 4.29 (2H, q, J=7.0 Hz), 4.67 (2H, d, J=6.0 Hz), 4.94-5.08 (1H, m), 5.94 (2H, s), 6.77-6.90 (3H, m), 6.95 (1H, t, J=7.6 Hz), 7.10-7.30 (2H, m), 8.25 (1H, d, J=8.2 Hz), 8.48 (1H, br t, J=7.0 Hz), 8.76 (1H, s)

Reference Example 8-1

5-methoxy-2,3-dihydro-1H-indole

[0184] To a solution of 5-methoxyindole (528 mg, 3.6 mmol) in acetic acid (5 mL) was added sodium cyanoborohydride (452 mg, 7.2 mmol) by small portions at room temperature and the mixture was stirred for 18 h *in situ*. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate solution (×3) and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give almost pure title compound (503 mg, 94%).

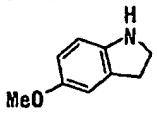
[0185] In the same manner as in Reference Example 8-1, compounds of Reference Examples 8-2 to 8-9 were synthesized.

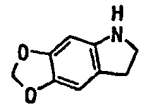
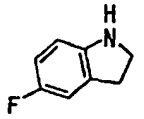
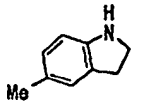
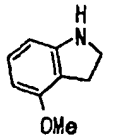
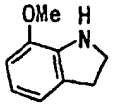
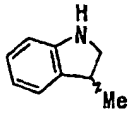
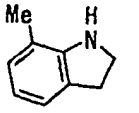
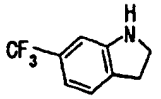
Reference Example 8-2: 6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indole

Reference Example 8-3: 5-fluoro-2,3-dihydro-1H-indole
Reference Example 8-4: 5-methyl-2,3-dihydro-1H-indole
Reference Example 8-5: 4-methoxy-2,3-dihydro-1H-indole
Reference Example 8-6: 7-methoxy-2,3-dihydro-1H-indole
Reference Example 8-7: (RS)-3-methyl-2,3-dihydro-1H-indole
Reference Example 8-8: 7-methyl-2,3-dihydro-1H-indole
Reference Example 8-9: 6-(trifluoromethyl)-2,3-dihydro-1H-indole

[0186] Respective structural formulas and NMR data are shown in the following Table.

[Table 25]

Reference Example No.	Structural Formula	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
8-1		94	2.94 (2H, t, J=8.0 Hz), 3.81 (3H, s), 4.30 (2H, t, J=8.4 Hz), 6.73-6.82 (2H, m), 8.39 (1H, br d, J=8.0 Hz), 8.81 (1H, s)

8-2		80	2.94 (2H, t, J=8.4 Hz), 3.56 (2H, t, J=8.4 Hz), 5.86 (2H, s), 6.32 (1H, s), 6.65 (1H, s)
8-3		100	3.02 (2H, t, J=8.4 Hz), 3.57 (2H, t, J=8.0 Hz), 6.55 (1H, dd, J=4.8, 8.4 Hz), 6.71 (1H, dt, J=2.6, 8.8 Hz), 6.84 (1H, d, J=8.8 Hz)
8-4		100	2.28 (3H, s), 3.04 (2H, t, J=8.0 Hz), 3.61 (2H, t, J=8.0 Hz), 6.25 (1H, d, J=7.6 Hz), 6.90 (1H, d, J=8.0 Hz), 7.01 (1H, s)
8-5		100	2.99 (2H, t, J=8.4 Hz), 3.58 (2H, t, J=8.0 Hz), 3.82 (3H, s), 6.35 (2H, t, J=8.0 Hz), 7.02 (1H, t, J=7.8 Hz)
8-6		100	3.06 (2H, t, J=8.2 Hz), 3.59 (2H, t, J=8.2 Hz), 3.82 (3H, s), 6.64-6.84 (3H, m)
8-7		100	1.32 (3H, d, J=6.8 Hz), 3.11 (1H, t, J=8.4 Hz), 3.37 (1H, q, J=7.8 Hz), 3.70 (1H, t, J=8.4 Hz), 6.65 (1H, d, J=7.6 Hz), 6.74 (1H, t, J=7.4 Hz), 6.98-7.13 (2H, m)
8-8		100	2.15 (3H, s), 3.06 (2H, t, J=8.4 Hz), 3.58 (2H, t, J=8.4 Hz), 6.68 (1H, t, J=7.2 Hz), 6.87 (1H, d, J=7.0 Hz), 6.99 (1H, d, J=7.6 Hz)
8-9		100	3.26 (2H, t, J=8.8 Hz), 4.14 (2H, J=8.6 Hz), 7.26 (2H, s), 8.48 (1H, s)

Reference Example 9-1

(RS)-2-hydroxymethylindoline

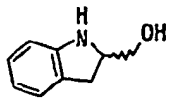
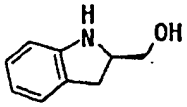
[0187] To a solution of (RS)-indoline-2-carboxylic acid (8.16 g, 50 mmol) in tetrahydrofuran (50 ml) was added under ice-cooling lithium aluminum hydride (5.7 g, 150 mmol) and the mixture was stirred at 60°C for 18 h. The reaction mixture was stirred under ice-cooling and ethanol and 1N hydrochloric acid were added. The precipitate was filtered off and the mother liquor was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was applied to silica gel column chromatography and eluted with ethyl acetate-hexane (1:4-1:1) to give the title compound (4.8 g, 64%).

[0188] In the same manner as in Reference Example 9-1, a compound of Reference Example 9-2 was synthesized from (S)-indoline-2-carboxylic acid.

Reference Example 9-2: (S)-2-hydroxymethylindoline

[0189] Respective structural formulas and NMR data are shown in the following Table.

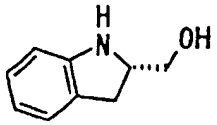
[Table 26]

Reference Example No.	Structural Formula	Yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
9-1		64	1.83 (1H, dd, J=7.8, 15.8 Hz), 3.12 (1H, dd, J=9.0, 15.6 Hz), 3.58 (1H, dd, J=6.2, 10.6 Hz), 3.73 (1H, dd, J=3.6, 10.6 Hz), 3.98-4.15 (1H, m), 6.60-6.77 (2H, m), 6.95-7.13 (2H, m)
9-2		100 (crude)	

Reference Example 10

(R)-2-hydroxymethylindoline

[0190]



[0191] To a solution of (R)-mandelic acid (8.72 g, 58 mmol) in ether (100 ml) was added (RS)-2-hydroxymethylindoline (4.27 g, 28.6 mmol), and the mixture was stirred for a while and concentrated under reduced pressure until the amount of the solvent became 50 ml. The precipitated crystals were collected by filtration and washed with cold ether. This operation was repeated twice to give (R)-2-hydroxymethylindoline (R)-dimandelate (5.3 g). To the thus-obtained mandelate (5.3 g) was added 0.5N aqueous sodium hydroxide solution and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the title compound (1.5 g, 72%).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.83 (1H, dd, J=7.8, 15.8 Hz), 3.12 (1H, dd, J=9.0, 15.6 Hz), 3.58 (1H, dd, J=6.2, 10.6 Hz), 3.73 (1H, dd, J=3.6, 10.6 Hz), 3.98-4.15 (1H, m), 6.60-6.77 (2H, m), 6.95-7.13 (2H, m)

Reference Example 11-1

(R)-1-p-tosyl-2-p-tosyloxymethylindoline

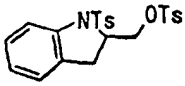
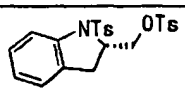
[0192] To a solution of (R)-2-hydroxymethylindoline (2.4 g, 16.1 mmol) in pyridine (25 mL) was added under ice-cooling p-toluenesulfonyl chloride (6.9 g, 36.2 mmol) and the mixture was stirred at room temperature for 18 h. The solvent was concentrated under reduced pressure and to the obtained residue were added ethyl acetate and 1N hydrochloric acid. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was applied to silica gel column chromatography and eluted with ethyl acetate-hexane (1:4-1:1) to give the title compound (10.5 g, 70%).

[0193] In the same manner as in Reference Example 11-1, a compound of Reference Example 11-2 was synthesized from (S)-2-hydroxymethylindoline.

Reference Example 11-2: (S)-1-p-tosyl-2-p-tosyloxymethyl-indoline

[0194] Respective structural formulas and NMR data are shown in the following Table.

[Table 27]

Reference Example No.	Structural Formula	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
11-1		79	2.35 (3H, s), 2.47 (3H, s), 2.80-2.09 (2H, m), 4.01 (1H, dd, J=8.4, 9.6 Hz), 4.24-4.44 (2H, m), 7.03 (2H, d, J=4.4 Hz), 7.12-7.28 (3H, m), 7.36 (2H, d, J=8.4 Hz), 7.48 (2H, d, J=8.4 Hz), 7.58 (1H, d, J=7.6 Hz), 7.78 (2H, d, J=6.6 Hz)
11-2		70	

Reference Example 12-1

(S)-2-methylindoline

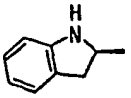
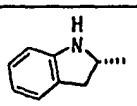
[0195] To a solution of (R)-1-p-tosyl-2-p-tosyloxymethylindoline (5.8 g, 12.7 mmol) in tetrahydrofuran (50 mL) was added under ice-cooling lithium aluminum hydride (2.4 g, 63.5 mmol) and the mixture was stirred at 60°C for 3 days. The reaction mixture was stirred under ice-cooling and ethanol and 1N aqueous sodium hydroxide solution were added. The precipitate was filtered off and the mother liquor was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was applied to silica gel column chromatography and eluted with ethyl acetate-hexane (1:4) to give the title compound (1.5 g, 90%).

[0196] In the same manner as in Reference Example 12-1, a compound of Reference Example 12-2 was synthesized from (S)-1-p-tosyl-2-p-tosyloxymethylindoline.

Reference Example 12-2: (R)-2-methylindoline

[0197] Respective structural formulas and NMR data are shown in the following Table. Optical purity was determined by measuring the amide, which is obtained by reacting (S)-2-methylindoline and (R)-2-methylindoline respectively with (S)-α-methoxy-α-trifluoromethylphenylacetyl chloride in pyridine, for ^{1}H-NMR and calculating the integral ratio of the 2-position methyl group.

[Table 28]

Reference Example No.	Structural Formula	yield (%)	Optical purity (ee, %)	^{1}H-NMR(δ ppm, $CDCl_3$)
12-1		90	80	1.29 (3H, d, J=6.2 Hz), 2.63 (1H, dd, J=7.6, 15.4 Hz), 3.14 (1H, dd, J=8.4, 15.4 Hz), 3.90-4.08 (1H, m), 6.57-6.73 (2H, m), 6.94-7.08 (2H, m)
12-2		89	>95	

Reference Example 13-1

(2,3-dihydrobenzo[b]furan-5-yl)methanol

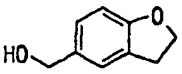
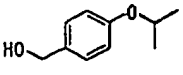
[0198] To a solution of 2,3-dihydrobenzo[b]furan-5-carboxylic acid (1.64 g, 10 mmol) in tetrahydrofuran (10 mL) was added under ice-cooling lithium aluminum hydride (949 mg, 25 mmol) and the mixture was stirred at 60°C for 1 h. The reaction mixture was stirred under ice-cooling and methanol and 1N hydrochloric acid were added. The precipitate was filtered off and the mother liquor was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (1.5 g, 100%).

[0199] In the same manner as in Reference Example 13-1, a compound of Reference Example 13-2 was synthesized from 4-isopropoxybenzoic acid.

Reference Example 13-2: 4-isopropoxybenzyl alcohol

[0200] Respective structural formulas and NMR data are shown in the following Table.

[Table 29]

Reference Example No.	Structural Formula	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
13-1		100	1.52 (1H, br t, J=8.0 Hz), 3.21 (2H, t, J=8.8 Hz), 4.52-4.63 (4H, m), 6.76 (1H, d, J=8.0 Hz), 7.10 (1H, d, J=8.2 Hz), 7.22 (1H, s)
13-2		100	1.33 (6H, d, J=5.8 Hz), 1.52 (1H, br t, J=5.6 Hz), 4.55 (1H, sevenplet, J=6.0 Hz), 4.61 (2H, d, J=5.4 Hz), 6.87 (2H, d, J=6.6 Hz), 7.27 (2H, d, J=6.6 Hz)

Reference Example 14-1

(2,3-dihydrobenzo[b]furan-5-yl)methyl chloride

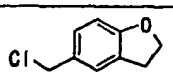
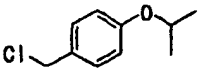
[0201] To a solution of (2,3-dihydrobenzo[b]furan-5-yl)methanol (1.5 g, 10 mmol) in dichloromethane (10 mL) were added under ice-cooling triethylamine (1.67 mL, 12 mmol) and methanesulfonyl chloride (0.85 mL, 10 mmol) and the mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (1.6 g, 100%).

[0202] In the same manner as in Reference Example 14-1, a compound of Reference Example 14-2 was synthesized from 4-isopropoxybenzyl alcohol.

Reference Example 14-2: 4-isopropoxybenzyl chloride

[0203] Respective structural formulas and NMR data are shown in the following Table.

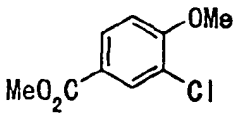
[Table 30]

Reference Example No.	Structural Formula	yield (%)	^{1}H-NMR (δ ppm, $CDCl_3$)
14-1		100	3.21 (2H, t, J=8.4 Hz), 4.50-4.62 (4H, m), 6.75 (1H, d, J=8.0 Hz), 7.08 (1H, d, J=8.0 Hz), 7.23 (1H, s)
14-2		100	1.33 (6H, d, J=5.0 Hz), 4.45-4.62 (3H, m), 6.85 (2H, d, J=6.6 Hz), 7.29 (2H, d, J=6.6 Hz)

Reference Example 15

methyl 3-chloro-4-methoxybenzoate

[0204]



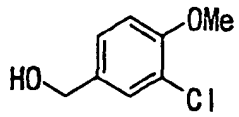
[0205] To a solution of 3-chloro-4-hydroxybenzoic acid (3.45 g, 20 mmol) in N,N-dimethylformamide (10 mL) were added potassium carbonate (6.9 g, 50 mmol) and methyl iodide (large excess) and the mixture was stirred at 60°C for 2 h. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (4.0 g, 100%).

^{1}H-NMR (δ ppm, $CDCl_3$) : 3.90 (3H, s), 3.97 (3H, s), 6.95 (1H, d, J=8.8 Hz), 7.95 (1H, dd, J=2.2, 8.8 Hz), 8.06 (1H, d, J=2.2 Hz)

Reference Example 16

3-chloro-4-methoxybenzyl alcohol

[0206]

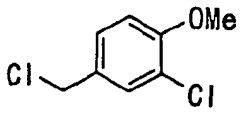


[0207] To a solution of methyl 3-chloro-4-methoxybenzoate (1.2 g, 6 mmol) in tetrahydrofuran (10 ml) was added under ice-cooling lithium aluminum hydride (455 mg, 12 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was stirred under ice-cooling and 0.1N hydrochloric acid was added. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (1.1 g, 100%).
^{1}H-NMR (δ ppm, $CDCl_3$): 1.69 (1H, br t, J=6.0 Hz), 3.91 (3H, s), 4.61 (2H, d, J=5.4 Hz), 6.91 (1H, d, J=8.4 Hz), 7.22 (1H, dd, J=2.2, 8.4 Hz), 7.39 (1H, d, J=2.2 Hz)

Reference Example 17

3-chloro-4-methoxybenzyl chloride

[0208]



[0209] To a solution of 3-chloro-4-methoxybenzyl alcohol (1.1 g, 6 mmol) in tetrahydrofuran (5 mL) were added under ice-cooling triethylamine (1.67 mL, 12 mmol) and methanesulfonyl chloride (0.51 ml, 6 mmol) and the mixture was stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (700 mg, 61%).
^{1}H-NMR (δ ppm, $CDCl_3$): 3.91 (3H, s), 4.52 (2H, s), 6.90 (1H, d, J=8.4 Hz), 7.25 (1H, dd, J=2.2, 8.8 Hz), 7.42 (1H, d, J=2.2 Hz)

Reference Example 18-1

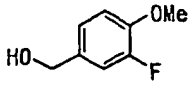
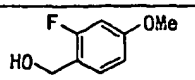
3-fluoro-4-methoxybenzyl alcohol

[0210] To a solution of 3-fluoro-4-methoxybenzaldehyde (1 g, 6.5 mmol) in methanol (15 mL) was added under ice-cooling sodium borohydride (378 mg, 10 mmol) and the mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (1 g, 100%).

[0211] In the same manner as in Reference Example 18-1, a compound of Reference Example 18-2 was synthesized from 2-fluoro-4-methoxybenzaldehyde.
Reference Example 18-2: 2-fluoro-4-methoxybenzyl alcohol

[0212] Respective structural formulas and NMR data are shown in the following Table.

[Table 31]

Reference Example No.	Structural Formula	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
18-1		100	1.64 (1H, br t, J=5.8 Hz), 3.89 (3H, s), 4.62 (2H, d, J=5.8 Hz), 6.94 (1H, t, J=8.8 Hz), 7.00-7.15 (2H, m)
18-2		47	1.69 (1H, t, J=5.6 Hz), 3.80 (3H, s), 4.67 (2H, d, J=5.8 Hz), 6.58-6.72 (2H, m), 7.30 (1H, t, J=8.8 Hz)

Reference Example 19-1

3-fluoro-4-methoxybenzyl chloride

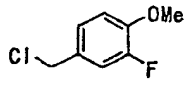
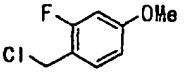
[0213] To a solution of 3-fluoro-4-methoxybenzyl alcohol (1 g, 6.5 mmol) in dichloromethane (10 mL) were added under ice-cooling triethylamine (1.8 mL, 13 mmol) and methanesulfonyl chloride (0.60 mL, 7 mmol) and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (1.1 g, 100%).

[0214] In the same manner as in Reference Example 19-1, a compound of Reference Example 17-2 was synthesized from 2-fluoro-4-methoxybenzyl alcohol.

Reference Example 19-2: 2-fluoro-4-methoxybenzyl chloride

[0215] Respective structural formulas and NMR data are shown in the following Table.

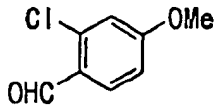
[Table 32]

Reference Example No.	Structural Formula	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
19-1		100	3.89 (3H, s), 4.53 (2H, s), 6.92 (1H, t, J=9.2 Hz), 7.00-7.15 (2H, m)
19-2		82	3.80 (3H, s), 4.61 (2H, s), 6.58-6.71 (2H, m), 7.30 (1H, t, J=8.4 Hz)

Reference Example 20

-chloro-4-methoxybenzaldehyde

[0216]

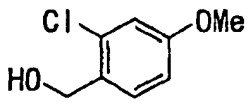


[0217] To a solution of 2-chloro-4-hydroxybenzaldehyde (2 g, 12.8 mmol) in N,N-dimethylformamide (25 mL) were added potassium carbonate (3.46 g, 25 mmol) and methyl iodide (large excess) and the mixture was stirred at room temperature for 18 h. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (1.55 g, 70%).
^{1}H-NMR (δ ppm, $CDCl_3$): 3.89 (3H, s), 6.84-6.95 (2H, m), 7.90 (1H, d, J=8.8 Hz), 10.33 (1H, s)

Reference Example 21

2-chloro-4-methoxybenzyl alcohol

[0218]

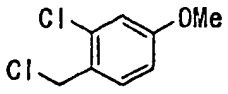


[0219] To a solution of 2-chloro-4-methoxybenzaldehyde (1.55 g, 9 mmol) in methanol (20 mL) was added under ice-cooling sodium borohydride (378 mg, 10 mmol) and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (1.5 g, 97%).
^{1}H-NMR (δ ppm, $CDCl_3$): 1.87 (1H, br t, J=6.2 Hz), 3.80 (3H, s), 4.71 (2H, d, J=5.8 Hz), 6.81 (1H, dd, J=2.6, 8.6 Hz), 6.93 (1H, d, J=2.6 Hz), 7.35 (1H, d, J=8.4 Hz)

Reference Example 22

2-chloro-4-methoxybenzyl chloride

[0220]

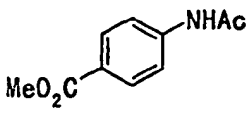


[0221] To a solution of 2-chloro-4-methoxybenzyl alcohol (1.5 g, 8.7 mmol) in dichloromethane (10 mL) were added under ice-cooling triethylamine (2.4 mL, 17.4 mmol) and methanesulfonyl chloride (0.74 mL, 9.5 mmol) and the mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (1.01 g, 61%).
^{1}H-NMR (δ ppm, $CDCl_3$) : 3.80 (3H, s), 4.67 (2H, s), 6.80 (1H, dd, J=2.6, 8.8 Hz), 6.95 (1H, d, J=2.6 Hz), 7.35 (1H, d, J=8.4 Hz)

Reference Example 23

methyl 4-acetamidebenzoate

[0222]

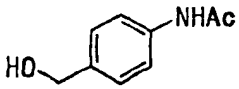


[0223] To a solution of methyl 4-aminobenzoate (7.56 g, 50 mmol) in tetrahydrofuran (50 mL) were added under ice-cooling triethylamine (10 mL, 73 mmol) and acetyl chloride (3.91 mL, 55 mmol) and the mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the obtained crystals were recrystallized from dichloromethane-isopropyl ether to give the title compound (6.4 g, 76%).
^{1}H-NMR (δ ppm, $CDCl_3$): 2.21 (3H, s), 3.90 (3H, s), 7.40-7.52 (1H, br), 7.59 (2h, d, J=8.8 Hz), 8.00 (2H, d, J=8.8 Hz)

Reference Example 24

4-hydroxymethylacetanilide

[0224]

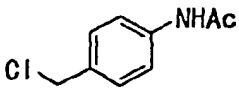


[0225] To a solution of methyl 4-acetamidebenzoate (483 mg, 2.5 mmol) in tetrahydrofuran (10 mL) was added under ice-cooling lithium aluminum hydride (190 mg, 5 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was stirred under ice-cooling and 1N hydrochloric acid was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (230 mg, 56%).
^{1}H-NMR (δ ppm, $CDCl_3$) : 2.02 (3H, s), 4.42 (2H, br s), 5.00-5.15 (1H, br), 6.53 (1H, br s), 7.22 (2H, d, J=8.8 Hz), 7.51 (2H, d, J=8.4 Hz)

Reference Example 25

4-chloromethylacetanilide

[0226]



[0227] To a solution of 4-hydroxymethylacetanilide (230 mg, 1.4 mmol) in tetrahydrofuran (5 mL) were added under ice-cooling triethylamine (0.39 mL, 2.8 mmol) and methanesulfonyl chloride (0.17 mL, 2 mmol) and the mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an almost pure title compound (200 mg, 78%).
^{1}H-NMR (δ ppm, $CDCl_3$): 2.18 (3H, s), 4.56 (2H, s), 7.28-7.38 (3H, m) , 7.50 (2H, d, J=8.6 Hz)

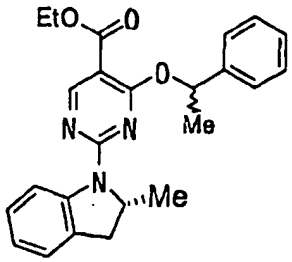
Reference Example 26

ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(RS)-1-phenylethoxy]-5-pyrimidinecarboxylate

Reference Example 27

ethyl 2-[(R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-4-[(RS)-1-phenylethoxy]-5-pyrimidinecarboxylate

[0228] In the same manner as in Reference Example 3-1 using ethyl 4-hydroxy-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate and ethyl 4-hydroxy-2-[(R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-5-pyrimidinecarboxylate as starting materials, compounds of Reference Examples 26 and 27 were synthesized.



[0229] Respective NMR data are shown in the following Table.

Reference Example No.	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
26	77	1.41 (3H, t, J=7.0 Hz), 1.73 (3H, d, J=8.8 Hz), 3.17 (2H, t, J=8.8 Hz), 4.22 (2H, t, J=8.4 Hz), 4.37 (2H, q, J=7.2 Hz), 6.34 (1H, q, J=6.2 Hz), 6.98 (1H, t, J=7.2 Hz), 7.16-7.40 (4H, m), 7.50 (2H, d, J=7.0 Hz), 8.00-8.40 (1H, br), 8.90 (1H, s)
27	94	1.30-1.52 (6H, m), 1.67-1.77 (3H, m), 2.67 (1H, d, J=15.0 Hz), 3.29-3.48 (1H, m), 4.37 (2H, q, J=7.0 Hz), 4.80-5.02 (1H, m), 6.32 (1H, t, J=6.0 Hz), 7.00 (1H, t, J=7.6 Hz), 7.13-7.53 (7H, m), 8.00-8.30 (1H, m), 8.89 (1H, s)

Example 1-1

t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl)carbonyl)amino]acetate

[0230] To a suspension of ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxylate (5.0 g, 13 mmol) in ethanol (25 mL) were added 10% aqueous sodium hydroxide solution (15 mL) and tetrahydrofuran (15 mL) and the mixture was heated under reflux for 30 min. The reaction mixture was allowed to cool to room temperature and 1N hydrochloric acid was added to adjust the reaction mixture to pH 5. The precipitated crystals were collected by filtration, washed several times with water, dried with heating under vacuum to give 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxylic acid (4.8 g, 100%) as crystals. To the obtained suspension of the obtained carboxylic acid (183 mg, 0.5 mmol), t-butyl glycine (89 mg, 0.53 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (102 mg, 0.53 mmol) in dichloromethane (2 mL) was added triethylamine (0.21 mL, 1.5 mmol) and the mixture was stirred at room temperature for 18 h. Water and ethyl acetate were added to the reaction mixture and the organic layer was concentrated under reduced pressure. The obtained residue was subjected to silica gel chromatography and eluted with ethyl acetate to give the title compound (210 mg, 88%).

[0231] In the same manner as in Example 1-1, compounds of Examples 1-2 to 1-46 were synthesized.

Example 1-2: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide
Example 1-3: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(3-methoxypropyl)-5-pyrimidinecarboxamide
Example 1-4: N-(2-cyanoethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide
Example 1-5: N-(2-cyanomethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide
Example 1-6: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-propyl-5-pyrimidinecarboxamide
Example 1-7: N-(2-amino-2-oxoethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide

Example 1-8: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 1-9: (RS)-1-({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl)carbonyl)-3-piperidinecarboxamide

Example 1-10: N-cyclohexyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide

Example 1-11: 2-(2,3-dihydro-1H-indol-1-yl)-N,N-diethyl-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide

Example 1-12: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-[3-(2-oxo-1-pyrrolizinyl)propyl]-5-pyrimidinecarboxamide

Example 1-13: methyl (2S)-1-({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy)-5-pyrimidinyl)carbonyl)-2-pyrrolidinecarboxylate

Example 1-14: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-hexyl-5-pyrimidinecarboxamide

Example 1-15: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

Example 1-16: 2-(2,3-dihydro-1H-indol-1-yl)-N-(2-ethoxyethyl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide

Example 1-17: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N,N-bis(2-hydroxyethyl)-5-pyrimidinecarboxamide

Example 1-18: {2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl}(4-hydroxy-1-piperidinyl)methanone

Example 1-19: {2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl} (1-pyrrolizinyl)methanone

Example 1-20: ethyl 1-({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl}carbonyl)-4-piperidinecarboxylate

Example 1-21: N-(1,3-benzodioxol-5-ylmethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide

Example 1-22: methyl (2S)-2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]-3-hydroxypropanoate

Example 1-23: 1-[4-({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl}carbonyl)-1-piperazinyl]-1-ethanone

Example 1-24: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(2-hydroxyethyl)-5-pyrimidinecarboxamide

Example 1-25: N-(2,5-difluorobenzyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide

Example 1-26: t-butyl 4-({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl)carbonyl)-1-piperazinecarboxylate

Example 1-27: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-[4-(trifluoromethyl)benzyl]-5-pyrimidinecarboxamide

Example 1-28: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(2-thienylmethyl)-5-pyrimidinecarboxamide

Example 1-29: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(2,2,2-trifluoroethyl)-5-pyrimidinecarboxamide

Example 1-30: N-[2-(acetylamino)ethyl]-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide

Example 1-31: ethyl 3-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]propanoate

Example 1-32: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N,N-dimethyl-5-pyrimidinecarboxamide

Example 1-33: (2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl)[(2S)-2-(hydroxymethyl)-pyrrolizinyl]methanone

Example 1-34: ethyl (2S)-2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl)carbonyl)amino]-4-(methylsulfanyl)butanoate

Example 1-35: {2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl}(4-methyl-1-piperazinyl)-methanone

Example 1-36: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(3-methoxyphenyl)-5-pyrimidinecarboxamide

Example 1-37: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-[2-(4-morpholinyl)ethyl]-5-pyrimidinecarboxamide

Example 1-38: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]acetate

Example 1-39: N-[4-(aminosulfonyl)phenethyl]-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide

Example 1-40: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 1-41: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(3-phenylpropyl)-5-pyrimidinecarboxamide

Example 1-42: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-phenethyl-5-pyrimidinecarboxamide

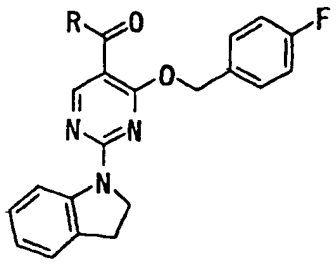
Example 1-43: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(2-furylmethyl)-5-pyrimidinecarboxamide

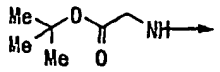
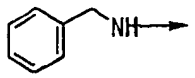
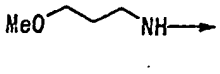
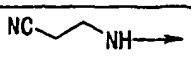
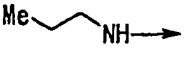
Example 1-44: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(1-naphthylmethyl)-5-pyrimidinecarboxamide

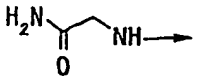
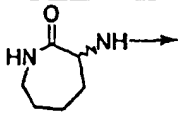
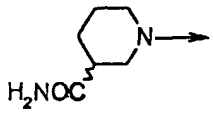
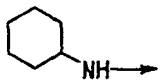
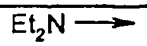
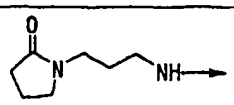
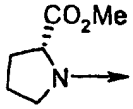
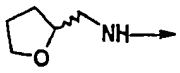
Example 1-45: 2-(2,3-dihydro-1H-indol-1-yl)-N-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide

Example 1-46: 2-(2,3-dihydro-1H-indol-1-yl)-N-(2,6-difluorobenzyl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxamide

[0232] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Tables.

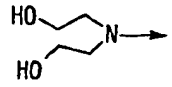
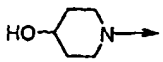
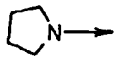
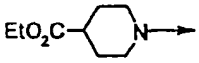
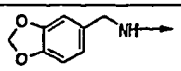
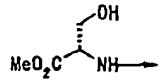
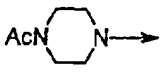
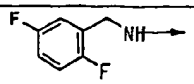
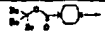
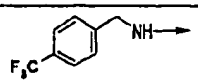


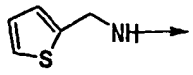
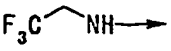
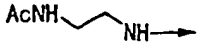
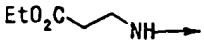
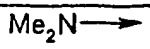
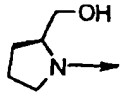
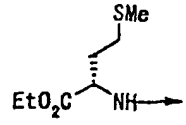
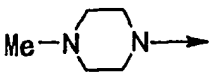
Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
1-1		88	479 $(M+H)^+$ 1.47 (9H, s), 3.22 (2H, t, J=8.8 Hz), 4.08 (2H, d, J=4.6 Hz), 4.30 (2H, t, J=7.8 Hz), 5.63 (2H, s), 6.95-7.30 (5H, m), 7.53 (2H, dd, J=5.8, 8.2 Hz)
1-2		83	455 $(M+H)^+$ 3.23 (2H, t, J=8.6 Hz), 4.32 (2H, t, J=8.0 Hz), 4.55 (2H, d, J=5.2 Hz), 5.49 (2H, s), 6.90-7.07 (3H, m), 7.10-7.32 (9H, m), 7.50-7.63 (1H, br), 8.20-8.45 (1H, br), 9.17 (1H, s)
1-3		91	437 $(M+H)^+$ 1.77 (2H, quintet, J=6.6 Hz), 3.17-3.26 (5H, m), 3.36 (2H, t, J=5.8 Hz), 3.48 (2H, q, J=5.4 Hz), 4.30 (2H, t, J=8.0 Hz), 5.59 (2H, s), 6.94-7.13 (5H, m), 7.19-7.64 (3H, m), 8.20-8.40 (1H, br), 9.13 (1H, s)
1-4		96	418 $(M+H)^+$
1-5		82	404 $(M+H)^+$
1-6		82	407 $(M+H)^+$ 0.79 (3H, t, J=7.8 Hz), 1.45 (2H, sextet, J=7.0 Hz), 3.17-3.38 (4H, m), 4.31 (2H, t, J=8.8 Hz), 5.55 (2H, s), 6.95-8.50 (8H, m), 8.24-8.43 (1H, br), 9.14 (1H, s)

1-7		19	422 (M+H)$^+$ 3.23 (2H, t, J=8.4 Hz), 4.10 (2H, d, J=5.2 Hz), 4.31 (2H, t, 10.8 Hz), 5.66 (2H, s), 6.00-6.10 (1H, br), 6.95-7.28 (5H, m), 7.50-7.60 (2H, m), 8.09 (1H, t, J=8.0 Hz), 8.20-8.42 (1H, br), 9.07 (1H, s)
1-8		28	476 (M+H)$^+$
1-9		23	476 (M+H)$^+$
1-10		35	447 (M+H)$^+$
1-11		33	421 (M+H)$^+$ 0.08-1.20 (6H, m), 3.10-3.25 (4H, m), 3.40-3.62 (2H, m), 4.27 (2H, t, J=9.0 Hz), 5.48 (2H, s), 6.93-7.13 (3H, m), 7.14-7.27 (2H, m), 7.41 (2H, dd, J=5.2, 10.4 Hz), 8.24-8.34 (2H, m)
1-12		49	490 (M+H)$^+$
1-13		76	477 (M+H)$^+$
1-14		42	449 (M+H)$^+$
1-15		33	449 (M+H)$^+$

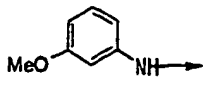
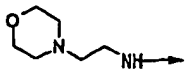
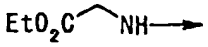
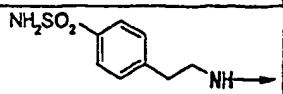
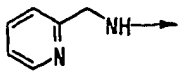
[Table 34]

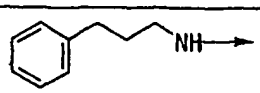
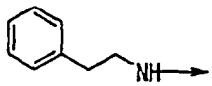
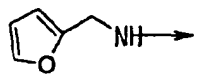
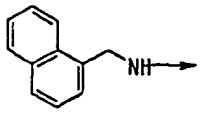
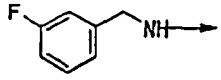
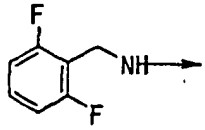
1-16		54	437 $(M+H)^+$ 1.10 (3H, t, J=7.0 Hz), 3.21 (2H, t, J=8.4 Hz), 3.40 (2H, q, J=7.0 Hz), 3.47-3.64 (4H, m), 4.29 (2H, t, J=8.4 Hz), 5.59 (2H, s), 6.93-7.30 (5H, m), 7.46 (2H, dd, J=5.0, 8.6 Hz), 7.70 (1H, br s), 8.20-8.45 (1H, br), 9.14 (1H, s)

1-17		19	453 $(M+H)^+$
1-18		27	449 $(M+H)^+$
1-19		43	419 $(M+H)^+$
1-20		56	505 $(M+H)^+$ 1.25 (3H, t, J=7.2 Hz), 1.40-2.05 (4H, m), 2.38-2.58 (1H, m), 2.83-3.12 (2H, m), 3.21 (2H, t, J=8.0 Hz), 3.40-3.75 (1H, m), 4.13 (2H, q, J=7.0 Hz), 4.27 (2H, t, J=9.2 Hz), 4.35-4.60 (1H, m), 5.49 (2H, s), 6.92-7.14 (3H, m), 7.14-7.25 (2H, m), 7.41 (2H, dd, J=5.0, 8.8 Hz), 8.29 (1H, d, J=8.8 Hz), 8.35 (1H, s)
1-21		28	499 $(M+H)^+$
1-22		55	467 $(M+H)^+$
1-23		58	476 $(M+H)^+$ 2.09 (3H, s), 3.00-3.80 (10H, m), 4.28 (2H, t, J=8.8 Hz), 5.49 (2H, s), 6.92-7.28 (5H, m), 7.40 (2H, dd, J=5.2, 9.0 Hz), 8.25 (1H, d, J=9.0 Hz), 8.40 (1H, s)
1-24		27	409 $(M+H)^+$
1-25		48	491 $(M+H)^+$
1-26		40	534 $(M+H)^+$
1-27		54	523 $(M+H)^+$ 3.23 (2H, t, J=8.0 Hz), 4.33 (2H, t, J=8.2 Hz), 4.60 (2H, d, 8.8 Hz), 5.52 (2H, s), 6.95-7.07 (4H, m), 7.20-7.35 (5H, m), 7.49-7.68 (3H, m), 8.20-8.45 (1H, br), 9.17 (1H, s)

1-28		47	461 $(M+H)^+$
1-29		40	447 $(M+H)^+$
1-30		94	450 $(M+H)^+$ 1.94 (3H, s), 3.21 (2H, t, J=8.4 Hz), 3.35-3.60 (4H, m), 4.28 (2H, t, J=8.4 Hz), 5.62 (2H, s), 6.30-6.45 (1H, br), 6.95-7.30 (5H, m), 7.47 (2H, dd, J=3.0, 8.4 Hz), 7.60-7.72 (1H, br), 8.15-8.45 (1H, br), 9.10 (1H, s)
1-31		71	465 $(M+H)^+$
1-32		71	393 $(M+H)^+$
1-33		35	449 $(M+H)^+$
1-34		69	524 $(M+H)^+$
1-35		25	448 $(M+H)^+$

[Table 35]

1-36		17	471 (M+H)$^+$
1-37		21	478 (M+H)$^+$
1-38		91	451 (M+H)$^+$
1-39		61	548 (M+H)$^+$
1-40		28	456 (M+H)$^+$ 3.22 (2H, t, J=8.8 Hz), 4.32 (2H, t, J=8.4 Hz), 4.73 (2H, d, J=4.8 Hz), 5.62 (2H, s), 6.97-7.10 (1H, m), 7.12-7.28 (5H, m), 7.49 (2H, dd, J=5.6, 8.8 Hz), 7.64 (1H, dt, J=1.8, 7.8 Hz), 8.29-8.50 (3H, m), 9.17 (1H, s)

1-41		52	483 (M+H)$^+$
1-42		51	469 (M+H)$^+$
1-43		59	445 (M+H)$^+$
1-44		70	505 (M+H)$^+$
1-45		58	473 (M+H)$^+$
1-46		59	491 (M+H)$^+$

Example 2

[0233] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-fluorobenzyl)oxy]-5-py-

rimidinecarboxylate as a starting material, compounds of Examples 2-1 to 2-5 were synthesized.

Example 2-1: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-fluorobenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]acetate

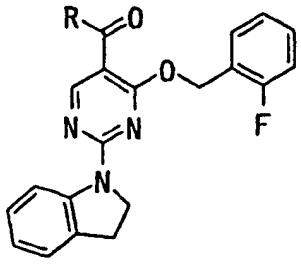
Example 2-2: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-fluorobenzyl)oxy]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

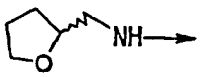
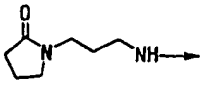
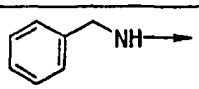
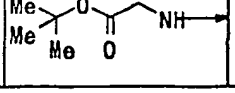
Example 2-3: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-fluorobenzyl)oxy]-N-[3-(2-oxo-1-pyrrolizinyl)propyl]-5-pyrimidinecarboxamide

Example 2-4: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-fluorobenzyl)oxy]-5-pyrimidinecarboxamide

Example 2-5: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-fluorobenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]acetate

[0234] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
2-1		51	450 $(M+H)^+$ 1.28 (3H, t, J=7.0 Hz), 3.22 (2H, t, J=8.4 Hz), 4.15-4.35 (6H, m), 5.76 (2H, s), 7.00 (1H, t, J=7.0 Hz), 7.08-7.45 (5H, m), 7.53 (1H, t, J=7.0 Hz), 7.92 (1H, t, J=7.0 Hz), 8.20-8.50 (1H, br), 9.13 (1H, s)
2-2		55	449 $(M+H)^+$
2-3		37	490 $(M+H)^+$
2-4		22	455 $(M+H)^+$
2-5		77	479 $(M+H)^+$

Example 3

[0235] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoromethyl)benzylloxy}-5-pyrimidinecarboxylate as a starting material, compounds of Examples 3-1 to 3-6 were synthesized.

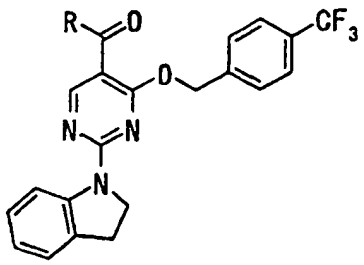
Example 3-1: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-4-{[4-(trifluoromethyl)benzyl]oxy)-5-pyrimidinecarboxamide

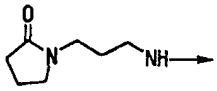
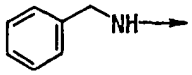
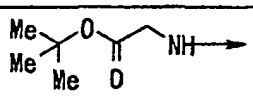
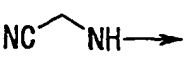
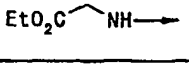
Example 3-2: 2-(2,3-dihydro-1H-indol-1-yl)-N-[3-(2-oxo-1-pyrrolizinyl)propyl]-4-{[4-(trifluoromethyl)benzyl]oxy)-5-pyrimidinecarboxamide

Example 3-3: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoromethyl)benzyl]oxy}-5-pyrimidinecarboxamide
Example 3-4: t-butyl 2-{[(2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoromethyl)benzyl]oxy)-5-pyrimidinyl)carbonyl]-amino}acetate
Example 3-5: N-(cyanomethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoromethyl)benzyl]oxy}-5-pyrimidinecarboxamide
Example 3-6: ethyl 2-{[(2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoromethyl)benzyl]oxy}-5-pyrimidinyl)carbonyl]-amino) acetate

[0236] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 37]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
3-1		36	499 $(M+H)^+$ 1.50-2.10 (4H, m), 3.15-3.40 (3H, m), 3.59-3.80 (3H, m), 3.90-4.10 (1H, m), 4.29 (2H, t, J=8.0 Hz), 5.68 (2H, s), 7.00 (1H, t, J=8.0 Hz), 7.15-7.30 (3H, m), 7.60-7.75 (4H, m), 8.20-8.45 (1H, br), 9.16 (1H, s)
3-2		26	540 $(M+H)^+$
3-3		28	505 $(M+H)^+$
3-4		57	529 $(M+H)^+$
3-5		57	454 $(M+H)^+$
3-6		20	501 $(M+H)^+$

Example 4

[0237] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 4-1 to 4-6 were synthesized.

Example 4-1: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-5-pyrimidinyl)carbonyl)amino]acetate

Example 4-2: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

Example 4-3: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

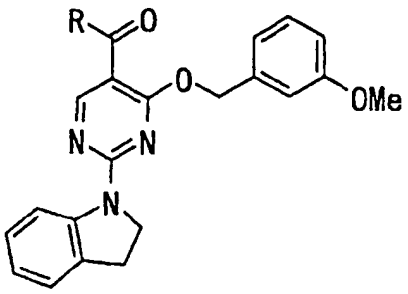
Example 4-4: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

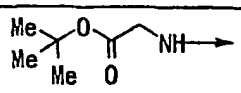
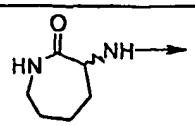
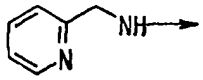
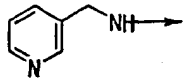
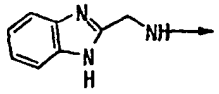
Example 4-5: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 4-6: N-(1H-benzimidazol-2-ylmethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

[0238] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 38]



Example No.	R	yield(%)	MASS spectrum (APCIMS, m/z)
4-1		75	491 $(M+H)^+$
4-2		70	461 $(M+H)^+$
4-3		49	488 $(M+H)^+$
4-4		69	468 $(M+H)^+$
4-5		34	467 $(M+H)^+$
4-6		40	506 $(M+H)^+$

Example 5

[0239] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-ethoxy-5-pyrimidinecarboxylate as a starting material, compounds of Examples 5-1 to 5-5 were synthesized.

Example 5-1: t-butyl 2-({[2-(2,3-dihydro-1H-indol-1-yl)-4-ethoxy-5-pyrimidinyl]carbonyl}amino)acetate

Example 5-2: 2-(2,3-dihydro-1H-indol-1-yl)-4-ethoxy-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

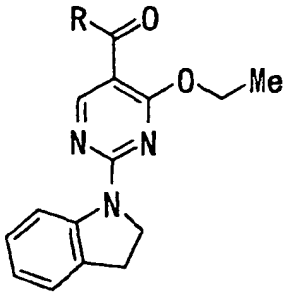
Example 5-3: t-butyl 3-({[2-(2,3-dihydro-1H-indol-1-yl)-4-ethoxy-5-pyrimidinyl]carbonyl}amino)propylcarbamate

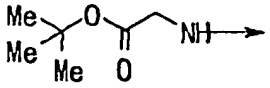
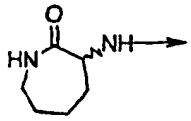
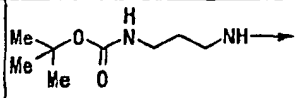
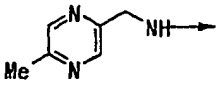
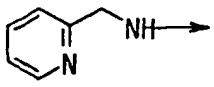
Example 5-4: 2-(2,3-dihydro-1H-indol-1-yl)-4-ethoxy-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 5-5: 2-(2,3-dihydro-1H-indol-1-yl)-4-ethoxy-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0240] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 39]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
5-1		62	399 $(M+H)^+$ 1.50-1.63 (12H, m), 3.21 (2H, t, J=8.0 Hz), 4.13 (2H, d, J=4.8 Hz), 4.31 (2H, t, J=8.0 Hz), 4.67 (2H, q, J=6.8 Hz), 7.00 (1H, t, J=6.8 Hz), 7.20-7.28 (2H, m), 8.05 (1H, br t, J=7.0 Hz), 8.10-8.42 (1H, br), 9.10 (1H, s)
5-2		75	396 $(M+H)^+$
5-3		68	442 $(M+H)^+$
5-4		78	391 $(M+H)^+$
5-5		87	376 $(M+H)^+$

Example 6

[0241] In the same manner as in Example 1-1 using ethyl 4-[(4-bromobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 6-1 to 6-6 were synthesized.

Example 6-1: 2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

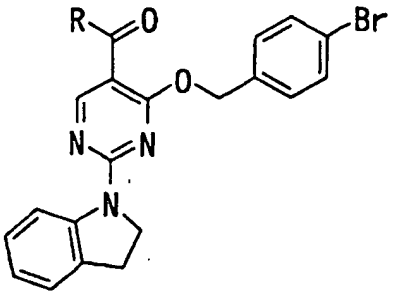
Example 6-2: t-butyl 3-({[4-[(4-bromobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)-propylcarbamate

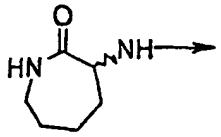
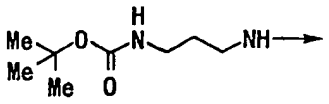
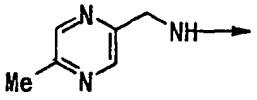
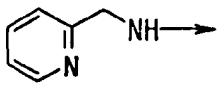
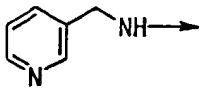
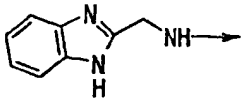
Example 6-3: 4-[(4-bromobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 6-4: 4-[(4-bromobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide
Example 6-5: 4-[(4-bromobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide
Example 6-6: N-(1H-benzimidazol-2-ylmethyl)-4-[(4-bromobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxamide

[0242] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 40]

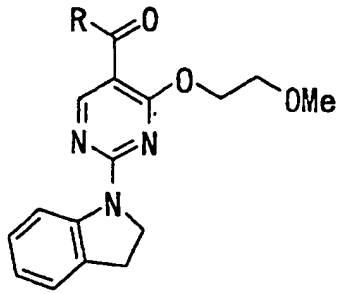


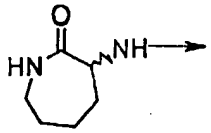
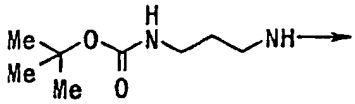
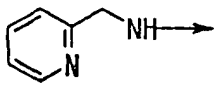
Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
6-1		34	537 $(M+H)^+$
6-2		48	583 $(M+H)^+$
6-3		55	532 $(M+H)^+$
6-4		48	517 $(M+H)^+$
6-5		67	517 $(M+H)^+$
6-6		92	556 $(M+H)^+$

Example 7

[0243] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-(2-methoxyethoxy)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 7-1 to 7-3 were synthesized.
Example 7-1: 2-(2,3-dihydro-1H-indol-1-yl)-4-(2-methoxyethoxy)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide
Example 7-2: t-butyl 3-({[2-(2,3-dihydro-1H-indol-1-yl)-4-(2-methoxyethoxy)-5-pyrimidinyl]carbonyl}amino)propylcarbamate
Example 7-3: 2-(2,3-dihydro-1H-indol-1-yl)-4-(2-methoxyethoxy)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide
[0244] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 41]



Example No.	R	yield(%)	MASS spectrum (APCIMS, m/z)
7-1		66	426 $(M+H)^+$
7-2		50	472 $(M+H)^+$
7-3		57	406 $(M+H)^+$

Example 8

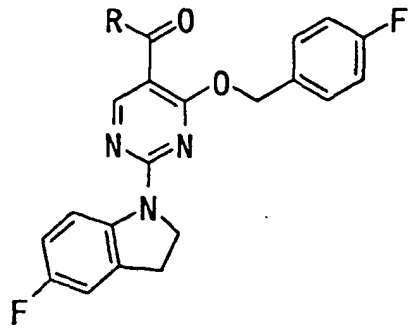
[0245] In the same manner as in Example 1-1 using ethyl 4-[(4-fluorobenzyl)oxy]-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 8-1 to 8-5 were synthesized.
Example 8-1: t-butyl 2-({[4-[(4-fluorobenzyl)oxy]-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)acetate
Example 8-2: (RS)-4-[(4-fluorobenzyl)oxy]-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide
Example 8-3: 4-[(4-fluorobenzyl)oxy]-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide
Example 8-4: 4-[(4-fluorobenzyl)oxy]-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarbox-

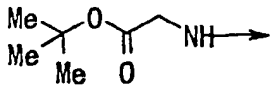
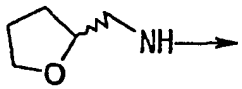
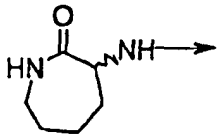
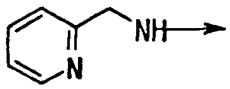
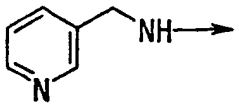
amide

Example 8-5: 4-[(4-fluorobenzyl)oxy]-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

[0246] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 42]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
8-1		82	497 $(M+H)^+$
8-2		53	467 $(M+H)^+$
8-3		76	494 $(M+H)^+$
8-4		76	474 $(M+H)^+$
8-5		67	474 $(M+H)^+$

Example 9

[0247] In the same manner as in Example 1-1 using ethyl 2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 9-1 to 9-5 were synthesized.

Example 9-1: t-butyl 2-[({2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy)-5-pyrimidinyl)carbonyl)-amino]acetate

Example 9-2: (RS)-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

Example 9-3: 2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecar-

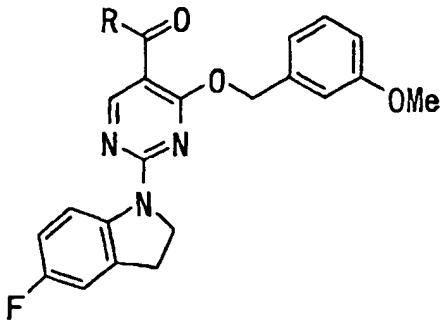
boxamide

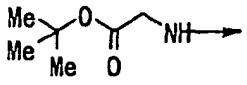
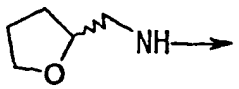
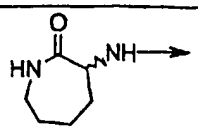
Example 9-4: 2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

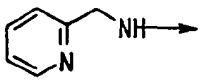
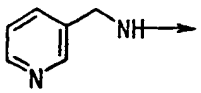
Example 9-5: 2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

[0248] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 43]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
9-1		85	509 $(M+H)^+$
9-2		55	479 $(M+H)^+$ 1.50-2.00 (4H, m), 3.20 (2H, t, J=8.0 Hz), 3.30-3.50 (1H, m), 3.60-3.70 (3H, m), 3.83 (3H, s), 3.90-4.05 (1H, m), 4.33 (2H, t, J=8.0 Hz), 5.70 (2H, d, J=2.2 Hz), 6.85-7.12 (4H, m), 7.20-7.35 (2H, m), 7.65-7.80 (1H, br), 8.20-8.40 (1H, br), 9.13 (1H, s)
9-3		74	506 $(M+H)^+$

9-4		70	486 (M+H)$^+$
9-5		70	486 (M+H)$^+$

Example 10

[0249] In the same manner as in Example 1-1 using ethyl (RS)-4-[(4-fluorobenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 10-1 to 10-5 were synthesized.

Example 10-1: t-butyl (RS)-2-({[4-[(4-fluorobenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl} amino) acetate

Example 10-2: (RS)-4-[(4-fluorobenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

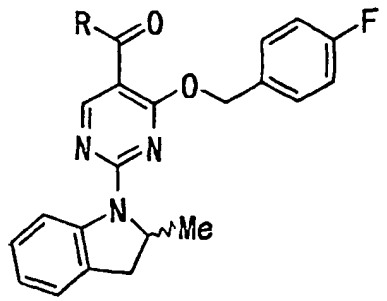
Example 10-3: (RS)-4-[(4-fluorobenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

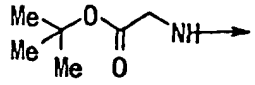
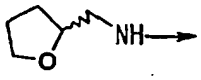
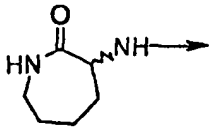
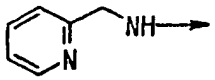
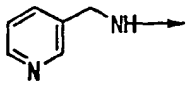
Example 10-4: (RS)-4-[(4-fluorobenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 10-5: (RS)-4-[(4-fluorobenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

[0250] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 44]

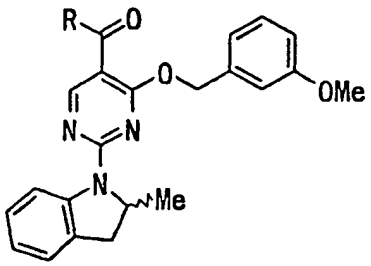


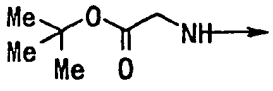
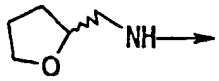
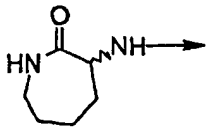
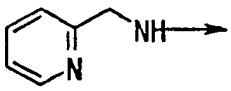
Example No.	R	yield(%)	MASS spectrum (APCIMS, m/z)
10-1		83	493 $(M+H)^+$
10-2		87	463 $(M+H)^+$
10-3		73	490 $(M+H)^+$
10-4		55	470 $(M+H)^+$
10-5		39	470 $(M+H)^+$

Example 11

[0251] In the same manner as in Example 1-1 using ethyl (RS)-4-[(3-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 11-1 to 11-5 were synthesized.
Example 11-1: t-butyl (RS)-2-({[4-[(3-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)acetate
Example 11-2: (RS)-4-[(3-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide
Example 11-3: (RS)-4-[(3-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide
Example 11-4: (RS)-4-[(3-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide
[0252] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 45]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
11-1		92	505 $(M+H)^+$
11-2		80	575 $(M+H)^+$
11-3		59	502 $(M+H)^+$
11-4		82	482 $(M+H)^+$ 1.35 (3H, d, J=6.2 Hz), 2.72 (1H, d, J=15.6 Hz), 3.44 (1H, dd, J=9.8, 16.2 Hz), 3.73 (3H, s), 4.74 (2H, d, J=4.6 Hz), 4.95-5.10 (1H, m), 5.62 (2H, s), 6.83-7.32 (8H, m), 7.62 (1H, dt, J=2.0, 7.6 Hz), 8.24-8.32 (2H, m), 8.53 (1H, br t, J=7.0 Hz), 9.17 (1H, s)

Example 12

[0253] In the same manner as in Example 1-1 using ethyl 2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-fluorobenzyl)-oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 12-1 to 12-6 were synthesized

Example 12-1: t-butyl [({2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl)carbonyl)-amino]acetate

Example 12-2: (RS)-2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl) -4-[(4-fluorobenzyl) oxy]-N- (2-oxo-3-azepanyl) -5-pyrimidinecarboxamide

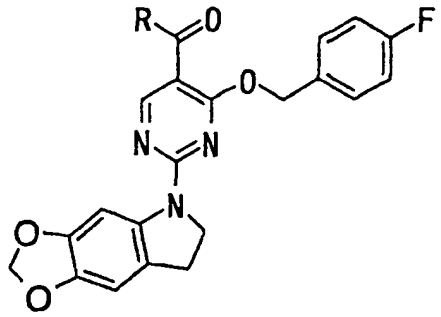
Example 12-3: (RS)-2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-fluorobenzyl)oxy]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

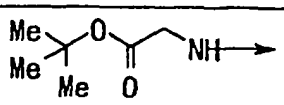
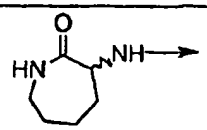
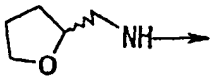
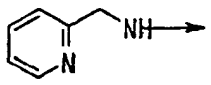
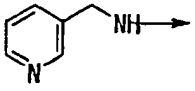
Example 12-4: 2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-fluorobenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 12-5: 2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-fluorobenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

[0254] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 46]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
12-1		54	523 $(M+H)^+$
12-2		39	520 $(M+H)^+$
12-3		12	493 $(M+H)^+$
12-4		40	500 $(M+H)^+$
12-5		49	500 $(M+H)^+$

Example 13

[0255] In the same manner as in Example 1-1 using ethyl 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 13-1 to 13-5 were synthesized.

Example 13-1: t-butyl 2-[({2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl}carbonyl)-amino]acetate

Example 13-2: (RS)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

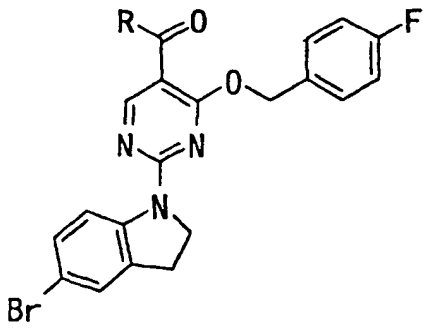
Example 13-3: (RS)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

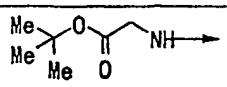
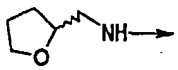
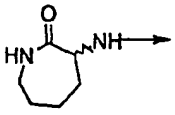
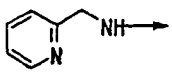
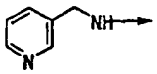
Example 13-4: 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 13-5: 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

[0256] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 47]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
13-1		62	558 $(M+H)^+$
13-2		44	528 $(M+H)^+$ 1.50-2.60 (4H, m), 3.15-3.40 (3H, m), 3.62-3.75 (3H, m), 3.75-4.02 (1H, m), 4.32 (2H, t, J=8.4 Hz), 5.50 (2H, s), 7.12 (2H, t, J=8.8 Hz), 7.30-7.40 (2H, m), 7.47 (2H, dd, J=6.0, 9.0 Hz), 7.60-7.75 (1H, m), 8.10-8.30 (1H, br), 9.14 (1H, s)
13-3		49	555 $(M+H)^+$
13-4		46	535 $(M+H)^+$
13-5		62	535 $(M+H)^+$

Example 14

[0257] In the same manner as in Example 1-1 using ethyl 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxyben-

zyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 14-1 to 14-6 were synthesized.

Example 14-1: t-butyl 2-[({2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-5-pyrimidinyl)carbonyl)-amino]acetate

Example 14-2: (RS)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

Example 14-3: (RS)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

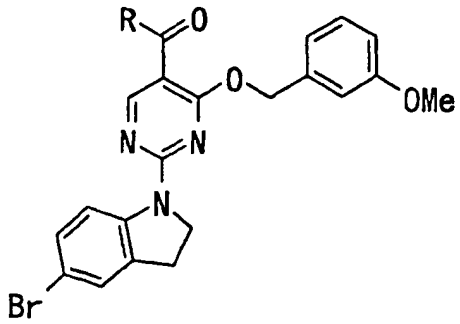
Example 14-4: 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-N-[2-(dimethylamino)ethyl]-4-[(3-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

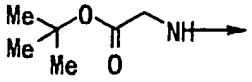
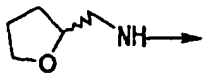
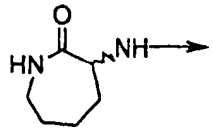
Example 14-5: 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

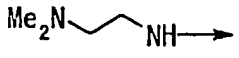
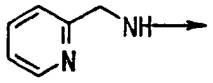
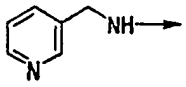
Example 14-6: 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(3-methoxybenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

[0258] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 48]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
14-1		60	570 $(M+H)^+$
14-2		50	540 $(M+H)^+$
14-3		28	567 $(M+H)^+$ 1.50-2.26 (6H, m), 3.14-3.40 (4H, m), 3.79 (3H, s), 4.29 (2H, t, J=8.8 Hz), 4.70-4.80 (1H, m),

			5.68 (2H, s), 5.97 (1H, t, J=7.0 Hz), 6.82-6.90 (1H, m), 7.08-7.14 (2H, m), 7.23-7.35 (3H, m), 8.00-8.35 (1H, br), 8.83 (1H, d, J=6.2 Hz), 9.09 (1H, s)
14-4		33	527 $(M+H)^+$
14-5		50	547 $(M+H)^+$
14-6		64	547 $(M+H)^+$

Example 15

[0259] In the same manner as in Example 1-1 using ethyl 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-ethoxy-5-pyrimidinecarboxylate as a starting material, compounds of Examples 15-1 to 15-4 were synthesized.

Example 15-1: (RS)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-ethoxy-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

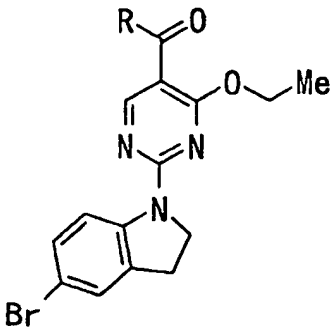
Example 15-2: t-butyl 2-({[2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-ethoxy-5-pyrimidinyl]carbonyl}amino)propylcarbamate

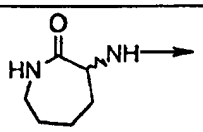
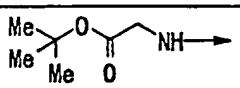
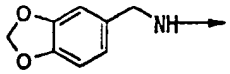
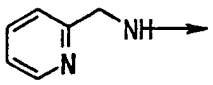
Example 15-3: N-(1,3-benzodioxol-5-ylmethyl)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-ethoxy-5-pyrimidinecarboxamide

Example 15-4: 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-ethoxy-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0260] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 49]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
15-1		25	475 $(M+H)^+$
15-2		46	521 $(M+H)^+$
15-3		56	498 $(M+H)^+$
15-4		63	455 $(M+H)^+$

Example 16

[0261] In the same manner as in Example 1-1 using ethyl 4-[(4-bromobenzyl)oxy]-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 16-1 to 16-5 were synthesized.

Example 16-1: (RS)-4-[(4-bromobenzyl)oxy]-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 16-2: t-butyl 3-({[4-[(4-bromobenzyl)oxy]-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)-propylcarbamate

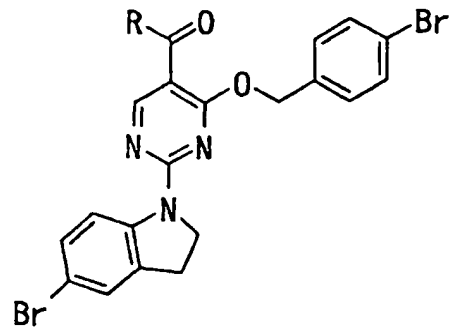
Example 16-3: 4-[(4-bromobenzyl)oxy]-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

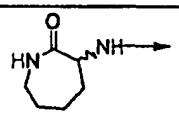
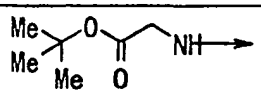
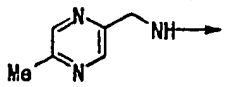
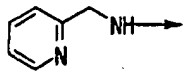
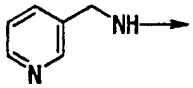
Example 16-4: 4-[(4-bromobenzyl)oxy]-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 16-5: 4-[(4-bromobenzyl)oxy]-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

[0262] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 50]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
16-1		29	616(M+H)$^+$ 1.40-2.30 (6H, m), 3.15-3.40 (4H, m), 4.28 (2H, t, J=8.4 Hz), 4.68-4.80 (1H, m), 5.64 (2H, s), 5.86-6.00 (1H, m), 7.20-7.38 (6H, m), 8.00-8.30 (1h, br), 8.76 (1H, d, J=7.0 Hz), 9.09 (1h, s)
16-2		45	662(M+H)$^+$
16-3		47	611(M+H)$^+$
16-4		42	596(M+H)$^+$
16-5		58	596(M+H)$^+$

Example 17

[0263] In the same manner as in Example 1-1 using ethyl 4-[(4-fluorobenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 17-1 to 17-4 were synthesized.

Example 17-1: t-butyl 2-({[4-[(4-fluorobenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl)-amino)acetate

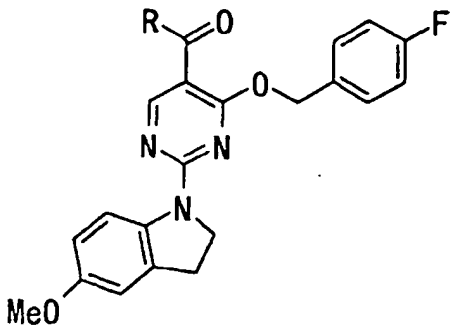
Example 17-2: (RS)-4-[(4-fluorobenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

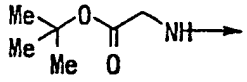
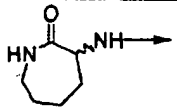
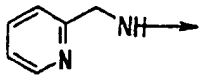
Example 17-3: (RS)-4-[(4-fluorobenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 17-4: 4-[(4-fluorobenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0264] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 51]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
17-1		60	509 $(M+H)^+$
17-2		66	479 $(M+H)^+$
17-3		67	506 $(M+H)^+$
17-4		83	486 $(M+H)^+$

Example 18

[0265] In the same manner as in Example 1-1 using ethyl 4-[(3-methoxybenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 18-1 to 18-5 were synthesized.

Example 18-1: t-butyl 2-({[4-[(3-methoxybenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}-amino)acetate

Example 18-2: (RS)-4-[(3-methoxybenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

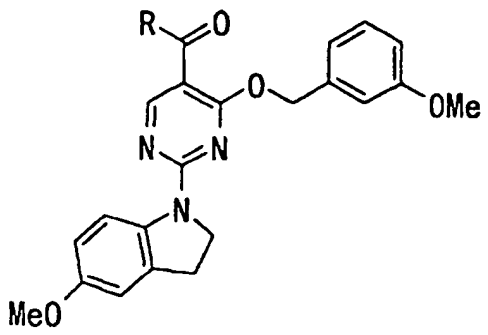
Example 18-3: (RS)-4-[(3-methoxybenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

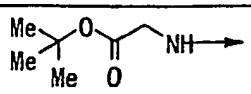
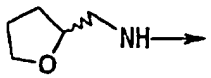
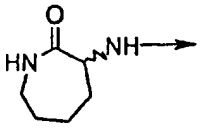
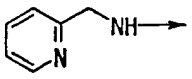
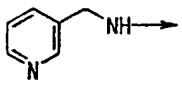
Example 18-4: 4-[(3-methoxybenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 18-5: 4-[(3-methoxybenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

[0266] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 52]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
18-1		96	521 $(M+H)^+$
18-2		56	491 $(M+H)^+$
18-3		84	518 $(M+H)^+$
18-4		50	498 $(M+H)^+$
18-5		43	498 $(M+H)^+$

Example 19

[0267] In the same manner as in Example 1-1 using ethyl 4-ethoxy-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 19-1 to 19-4 were synthesized.

Example 19-1: (RS)-4-ethoxy-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

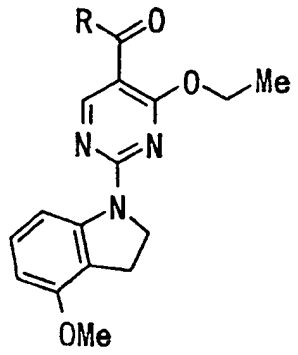
Example 19-2: t-butyl 3-({[4-ethoxy-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)propylcarbamate

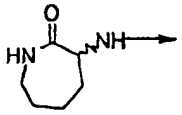
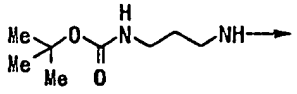
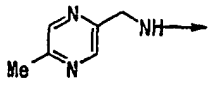
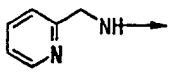
Example 19-3: 4-ethoxy-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 19-4: 4-ethoxy-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0268] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 53]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
19-1		75	426 $(M+H)^+$
19-2		69	472 $(M+H)^+$
19-3		88	421 $(M+H)^+$
19-4		89	406 $(M+H)^+$

Example 20

[0269] In the same manner as in Example 1-1 using ethyl 4-[(4-bromobenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 20-1 to 20-4 were synthesized.

Example 20-1: (RS)-4-[(4-bromobenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

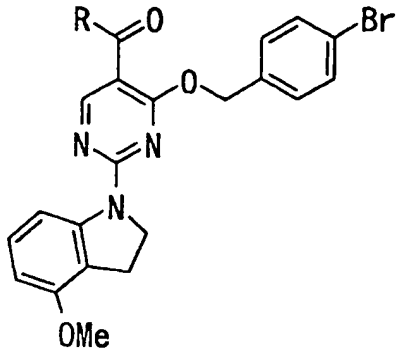
Example 20-2: t-butyl 3-({[4-[(4-bromobenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)-propylcarbamate

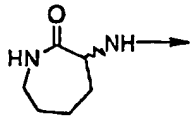
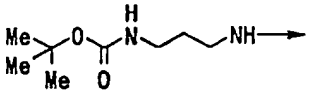
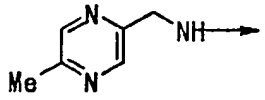
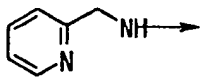
Example 20-3: 4-[(4-bromobenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 20-4: 4-[(4-bromobenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0270] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 54]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
20-1		44	567 $(M+H)^+$
20-2		50	613 $(M+H)^+$
20-3		68	562 $(M+H)^+$ 2.57 (3H, s), 3.13 (2H, t, J=8.0 Hz), 3.87 (3H, s), 4.31 (2H, t, J=10.0 Hz), 4.71 (2H, d, J=4.8 Hz), 5.55 (2H, s), 6.58 (1H, d, J=8.2 Hz), 7.21 (1H, t, J=8.0 Hz), 7.35 (2H, d, J=8.6 Hz), 7.51 (2H, d, J=8.4 Hz), 7.80-8.05 (1H, br), 8.08 (1H, s), 8.20-8.30 (1H, br), 8.46 (1H, s), 9.15 (1H, s)
20-4		66	547 $(M+H)^+$

Example 21

[0271] In the same manner as in Example 1-1 using ethyl 4-ethoxy-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 21-1 to 21-4 were synthesized.

Example 21-1: (RS)-4-ethoxy-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

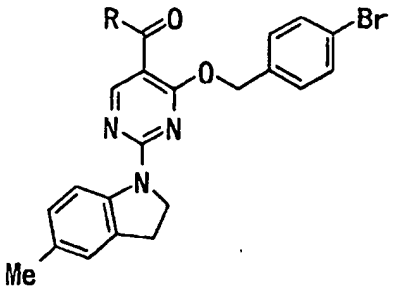
Example 21-2: t-butyl 3-({[4-ethoxy-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl)amino)propylcarbamate

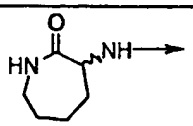
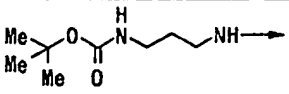
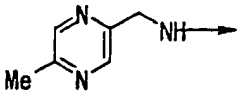
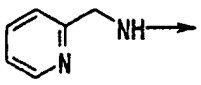
Example 21-3: 4-ethoxy-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 21-4: 4-ethoxy-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0272] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 55]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
21-1		68	410 $(M+H)^+$
21-2		57	456 $(M+H)^+$
21-3		85	405 $(M+H)^+$
21-4		95	390 $(M+H)^+$

Example 22

[0273] In the same manner as in Example 1-1 using ethyl 4-[(4-bromobenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 22-1 to 22-4 were synthesized.

Example 22-1: (RS)-4-[(4-bromobenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

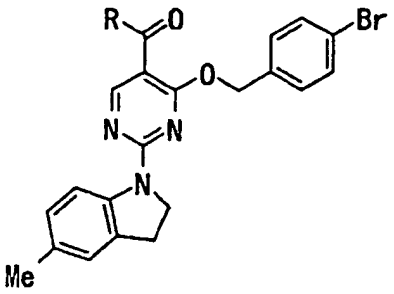
Example 22-2: t-butyl 3-({[4-[(4-bromobenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)-propylcarbamate

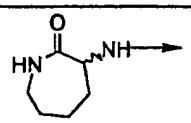
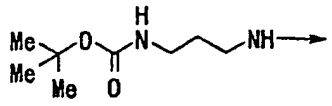
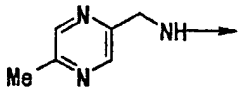
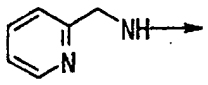
Example 22-3: 4-[(4-bromobenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 22-4: 4-[(4-bromobenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0274] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 56]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
22-1		33	551 $(M+H)^+$
22-2		63	597 $(M+H)^+$
22-3		75	546 $(M+H)^+$
22-4		69	531 $(M+H)^+$

Example 23

[0275] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 23-1 to 23-49 were synthesized.

Example 23-1: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinyl)carbonyl)amino]acetate

Example 23-2: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

Example 23-3: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[3-(2-oxo-1-pyrrolizinyl)propyl]-5-pyrimidinecarboxamide

Example 23-4: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-5: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinyl)carbonyl)amino]acetate

Example 23-6: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 23-7: 2-(2,3-dihydro-1H-indol-1-yl)-N-(2-ethoxyethyl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-8: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(4-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 23-9: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-oxo-3-piperidinyl)-5-pyrimidinecar-

boxamide

Example 23-10: 2-(2,3-dihydro-1H-indol-1-yl)-N-[3-(1H-imidazol-1-yl)propyl]-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-11: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 23-12: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[2-(2-pyridinyl)ethyl]-5-pyrimidinecarboxamide

Example 23-13: 2-(2,3-dihydro-1H-indol-1-yl)-N-(6-hydroxyhexyl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-14: N-[2-(diethylamino)ethyl]-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-15: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[1-(pyrrolizinyl)ethyl]-5-pyrimidinecarboxamide

Example 23-16: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 23-17: 2-(2,3-dihydro-1H-indol-1-yl)-N-(3-hydroxypropyl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-18: N-cyclopropyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-19: 2-(2,3-dihydro-1H-indol-1-yl)-N-[2-(dimethylamino)ethyl]-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-20: t-butyl 6-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]-hexylcarbamate

Example 23-21: t-butyl 4-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]-butylcarbamate

Example 23-22: t-butyl 3-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]-propylcarbamate

Example 23-23: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]-ethylcarbamate

Example 23-24: N-(1-benzyl-4-piperidinyl)-2-(2,3-dihydro-1H-indol-1-yl) -4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-25: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[3-(2-methyl-1-piperidinyl)propyl]-5-pyrimidinecarboxamide

Example 23-26: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[2-(4-morpholinyl)ethyl]-5-pyrimidinecarboxamide

Example 23-27: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[2-(1-piperidinyl)ethyl]-5-pyrimidinecarboxamide

Example 23-28: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-propinyl)-5-pyrimidinecarboxamide

Example 23-29: 2-(2,3-dihydro-1H-indol-1-yl)-N-[4-(dimethylamino)benzyl]-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-30: 2-(2,3-dihydro-1H-indol-1-yl)-N-[3-(dimethylamino)propyl]-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-31: N-(1,3-benzodioxol-5-ylmethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-32: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-thienylmethyl)-5-pyrimidinecarboxamide

Example 23-33: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2,2,2-trifluoroethyl)-5-pyrimidinecarboxamide

Example 23-34: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[3-(methylsulfanyl)propyl]-5-pyrimidinecarboxamide

Example 23-35: N-(cyanomethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-36: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-methoxyethyl)-5-pyrimidinecarboxamide

Example 23-37: N-[4-(diethylamino)phenyl]-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-38: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[2-(1-methyl-2-pyrrolizinyl)ethyl]-5-pyrimidinecarboxamide

Example 23-39: 2-(2,3-dihydro-1H-indol-1-yl)-N-(5-isoquinolinyl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-40: 2-(2,3-dihydro-1H-indol-1-yl)-N-(1H-indazol-5-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxam-

ide

Example 23-41: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[2-(2-oxo-1-imidazolidinyl)ethyl]-5-pyrimidinecarboxamide

Example 23-42: N-[2-(acetylamino)ethyl]-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-43: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 23-44: 2-(2,3-dihydro-1H-indol-1-yl)-N-(2-hydroxyethyl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-45: N-(1H-benzimidazol-2-ylmethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 23-46: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[4-(1,2,3-thiadiazol-4-yl)benzyl]-5-pyrimidinecarboxamide

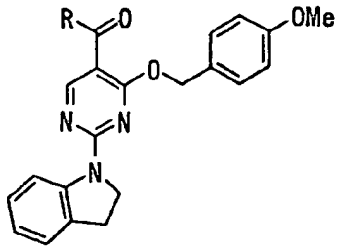
Example 23-47: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[2-(2-thienyl)ethyl]-5-pyrimidinecarboxamide

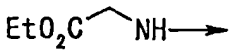
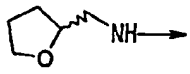
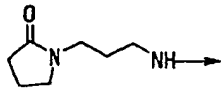
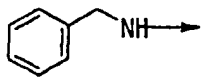
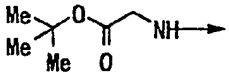
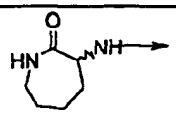
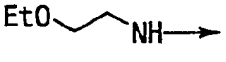
Example 23-48: N-(2-amino-2-oxoethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

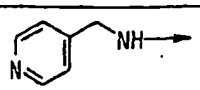
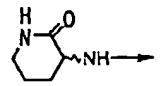
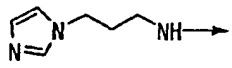
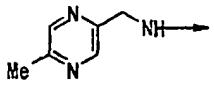
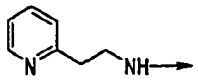
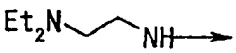
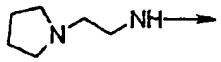
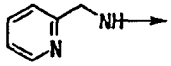
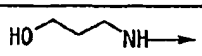
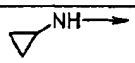
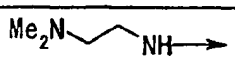
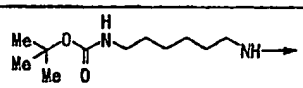
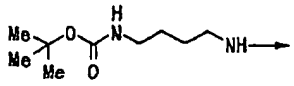
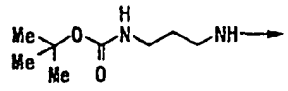
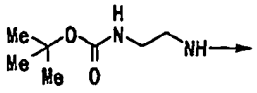
Example 23-49: N-(cycloheptyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

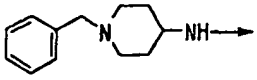
[0276] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 57]

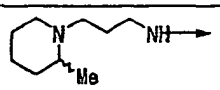
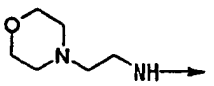
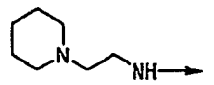
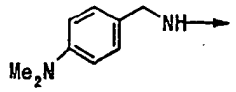
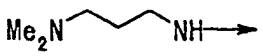
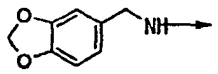
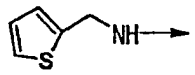
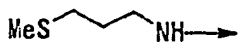
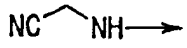
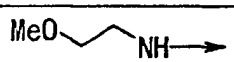
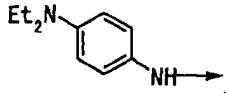
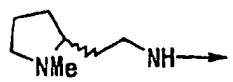
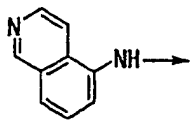


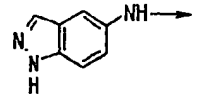
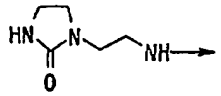
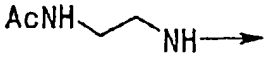
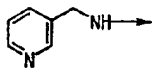
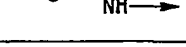
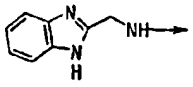
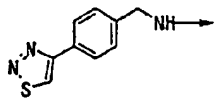
Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
23-1		47	463 $(M+H)^+$
23-2		48	461 $(M+H)^+$
23-3		32	502 $(M+H)^+$
23-4		35	467 $(M+H)^+$ 1.70 (2H, quintet, J=6.6 Hz), 2.02 (2H, quintet, J=7.6 Hz), 2.38 (2H, t, J=8.0 Hz), 3.15-3.40 (8H, m), 3.82 (3H, s), 4.31 (2H, t, J=8.8 Hz), 5.60 (2H, s), 6.87-7.04 (3H, m), 7.22 (2H, dd, J=2.6, 6.8 Hz), 7.45 (2H, d, J=8.6 Hz), 7.80 (1H, br t, J=6.8 Hz), 8.37 (1H, d, J=8.0 Hz), 9.09 (1H, s)
23-5		69	491 $(M+H)^+$
23-6		60	488 $(M+H)^+$
23-7		62	449 $(M+H)^+$

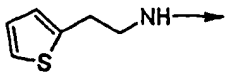
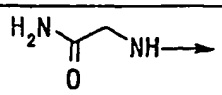
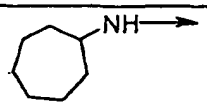
23-8		51	468 (M+H)$^+$
23-9		28	474 (M+H)$^+$
23-10		55	485 (M+H)$^+$
23-11		92	483 (M+H)$^+$
23-12		65	482 (M+H)$^+$
23-13		84	477 (M+H)$^+$
23-14		28	476 (M+H)$^+$
23-15		47	474 (M+H)$^+$
23-16		86	468 (M+H)$^+$
23-17		35	435 (M+H)$^+$
23-18		63	417 (M+H)$^+$
23-19		36	448 (M+H)$^+$
23-20		87	576 (M+H)$^+$
23-21		81	548 (M+H)$^+$
23-22		95	534 (M+H)$^+$
23-23		82	520 (M+H)$^+$

23-24		81	550 $(M+H)^+$

[Table 58]

23-25		26	516 (M+H)$^+$
23-26		80	490 (M+H)$^+$
23-27		75	488 (M+H)$^+$
23-28		57	415 (M+H)$^+$
23-29		82	510 (M+H)$^+$
23-30		50	462 (M+H)$^+$
23-31		70	511 (M+H)$^+$
23-32		70	473 (M+H)$^+$
23-33		72	459 (M+H)$^+$
23-34		54	465 (M+H)$^+$
23-35		73	416 (M+H)$^+$
23-36		61	435 (M+H)$^+$
23-37		38	524 (M+H)$^+$
23-38		27	488 (M+H)$^+$
23-39		37	504 (M+H)$^+$

23-40		37	493 (M+H)$^+$
23-41		38	489 (M+H)$^+$
23-42		71	462 (M+H)$^+$ 1.92 (3H, s), 3.22 (2H, t, J=8.6 Hz), 3.30-3.43 (2H, m), 3.44-3.53 (2H, m), 3.84 (3H, s), 4.32 (2H, t, J=8.0 Hz), 5.56 (2H, s), 6.32-6.43 (1H, br), 6.90-7.07 (3H, s), 7.18-7.26 (2H, m), 7.42 (2H, d, J=8.8 Hz), 7.60-7.75 (1H, br), 8.25-8.47 (1H, br), 9.09 (1H, s)
23-43		42	468 (M+H)$^+$
23-44		50	421 (M+H)$^+$
23-45		61	507 (M+H)$^+$ 3.21 (2H, t, J=8.4 Hz), 3.81 (3H, s), 4.30 (1H, t, J=8.8 Hz), 4.73 (2H, d, J=5.8 Hz), 5.54 (2H, s), 6.87 (2H, d, J=8.4 Hz), 7.01 (1H, t, J=8.0 Hz), 7.20-7.40 (7H, m), 7.50-7.64 (2H, m), 8.14 (1H, t, J=7.0 Hz), 8.20-8.50 (1H, br), 9.15 (1H, s)
23-46		80	551 (M+H)$^+$ 3.23 (2H, t, J=8.4 Hz), 3.72 (3H, s), 4.34 (2H, t, J=8.4 Hz), 4.61 (2H, d, J=5.0 Hz), 5.49 (2H, s), 6.82 (2H, d, J=8.8 Hz), 7.01 (1H, t, J=7.4 Hz), 7.20-7.32 (6H, m), 7.75 (1H, t,

			J=7.0 Hz), 7.93 (2H, d, J=8.0 Hz), 8.35-8.43 (1H, m), 8.68 (1H, s), 9.17 (1H, s)
23-47		90	487 $(M+H)^+$
23-48		60	434 $(M+H)^+$
23-49		73	473 $(M+H)^+$

Example 24

[0277] In the same manner as in Example 1-1 using ethyl 4-[(2,6-difluorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 24-1 to 24-5 were synthesized.

Example 24-1: (RS)-4-[(2,6-difluorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

Example 24-2: 4-[(2,6-difluorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-[3-(2-oxo-1-pyrrolizinyl)propyl]-5-pyrimidinecarboxamide

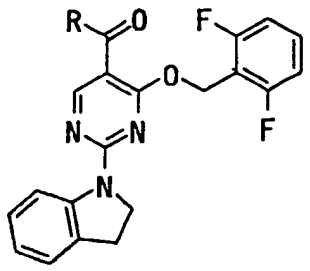
Example 24-3: N-benzyl-4-[(2,6-difluorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxamide

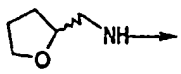
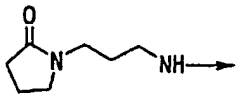
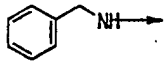
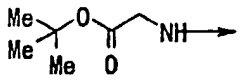
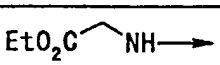
Example 24-4: t-butyl 2-({[4-[(2,6-difluorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)acetate

Example 24-5: ethyl 2-({[4-[(2,6-difluorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)acetate

[0278] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 59]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
24-1		31	467 $(M+H)^+$
24-2		28	508 $(M+H)^+$
24-3		49	473 $(M+H)^+$
24-4		83	497 $(M+H)^+$
24-5		60	469 $(M+H)^+$

Example 25

[0279] In the same manner as in Example 1-1 using ethyl 4-[(4-chlorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 25-1 to 25-7 were synthesized.

Example 25-1: 4-[(4-chlorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-ethoxyethyl)-5-pyrimidinecarboxamide

Example 25-2: 4-[(4-chlorobenzyl)oxy]-N-(cyanomethyl)-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxamide

Example 25-3: ethyl 2-({[4-[(4-chlorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)acetate

Example 25-4: (RS)-4-[(4-chlorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

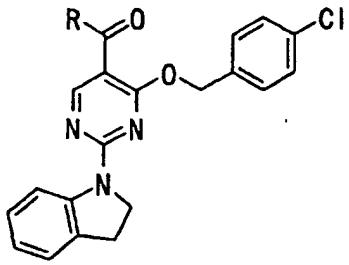
Example 25-5: 4-[(4-chlorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-[3-(2-oxo-1-pyrrolizinyl)propyl]-5-pyrimidinecarboxamide

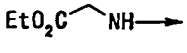
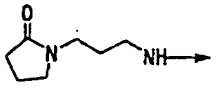
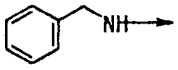
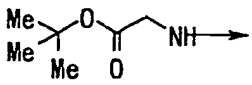
Example 25-6: N-benzyl-4-[(4-chlorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxamide

Example 25-7: t-butyl 2-({[4-[(4-chlorobenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)acetate

[0280] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 60]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
25-1		70	453 $(M+H)^+$ 1.09 (3H, t, J=7.0 Hz), 3.22 (2H, t, J=8.4 Hz), 3.30-3.65 (6H, m), 4.29 (2H, t, J=8.8 Hz), 5.60 (2H, s), 6.99 (1H, t, J=7.2 Hz), 7.15-7.48 (6H, m), 7.70 (1H, br s), 8.20-8.50 (1H, br), 9.15 (1H, s)
25-2		18	420 $(M+H)^+$
25-3		45	467 $(M+H)^+$
25-4		39	465 $(M+H)^+$
25-5		42	506 $(M+H)^+$
25-6		65	471 $(M+H)^+$
25-7		20	495 $(M+H)^+$

Example 26

[0281] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3,4-dimethylbenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 26-1 to 26-5 were synthesized.

Example 26-1: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(3,4-dimethylbenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]acetate

Example 26-2: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3,4-dimethylbenzyl)oxy]-5-pyrimidinecarboxamide

Example 26-3: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3,4-dimethylbenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecar-

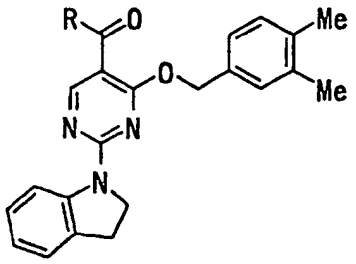
boxamide

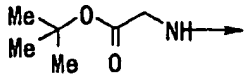
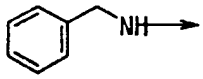
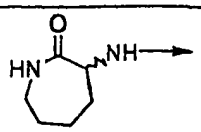
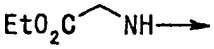
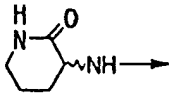
Example 26-4: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(3,4-dimethylbenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]acetate

Example 26-5: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3,4-dimethylbenzyl)oxy]-N-(2-oxo-3-piperidinyl)-5-pyrimidinecarboxamide

[0282] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 61]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
26-1		51	489 $(M+H)^+$
26-2		30	465 $(M+H)^+$
26-3		25	486 $(M+H)^+$
26-4		65	461 $(M+H)^+$
26-5		37	472 $(M+H)^+$

Example 27

[0283] In the same manner as in Example 1-1 using ethyl 4-(1,3-benzodioxol-5-ylmethoxy) -2- (2,3-dihydro-1H-indol-1-yl) -5-pyrimidinecarboxylate as a starting material, compounds of Examples 27-1 to 27-6 were synthesized.

Example 27-1: (RS)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 27-2: (RS)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-piperidinyl)-5-pyrimidinecarboxamide

Example 27-3: t-butyl 2-({[4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}-amino) acetate

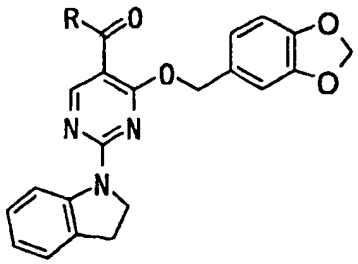
Example 27-4: 4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecar-

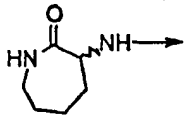
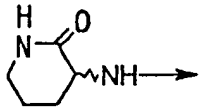
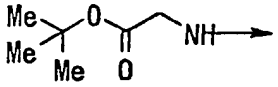
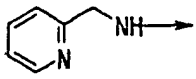
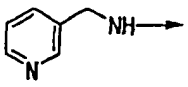
boxamide

Example 27-5: 4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

[0284] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 62]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
27-1		52	502 $(M+H)^+$
27-2		12	488 $(M+H)^+$
27-3		35	505 $(M+H)^+$
27-4		65	482 $(M+H)^+$
27-5		67	482 $(M+H)^+$

Example 28

[0285] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 28-1 to 28-4 were synthesized.

Example 28-1: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

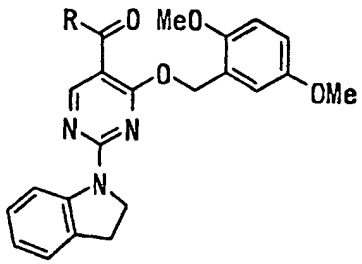
Example 28-2: t-butyl 3-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]-propylcarbamate

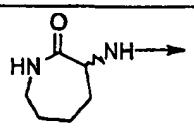
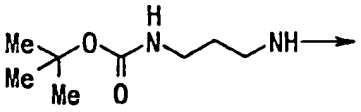
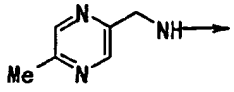
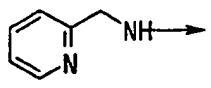
Example 28-3: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 28-4: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0286] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 63]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
28-1		30	518 $(M+H)^+$
28-2		68	564 $(M+H)^+$ 1.43 (9H, s), 1.63 (2H, quintet, J=6.2 Hz), 3.07 (2H, q, J=6.6 Hz), 3.22 (2H, t, J=8.4 Hz), 3.43 (2H, q, J=6.2 Hz), 3.74 (3H, s), 3.85 (3H, s), 4.32 (2H, t, J=8.4 Hz), 5.00-5.15 (1H, m), 5.62 (2H, s), 6.83-7.08 (4H, m), 7.20-7.25 (1H, m), 7.40-7.70 (1H, br), 8.30-8.43 (1H, br). 9.09 (1H, s)
28-3		80	513 $(M+H)^+$
28-4		50	498 $(M+H)^+$

Example 29

[0287] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-isopropoxybenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 29-1 to 29-6 were synthesized.

Example 29-1: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-isopropoxybenzyl)oxy]-N-(4-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 29-2: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-isopropoxybenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxa-

mide

Example 29-3: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-isopropoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

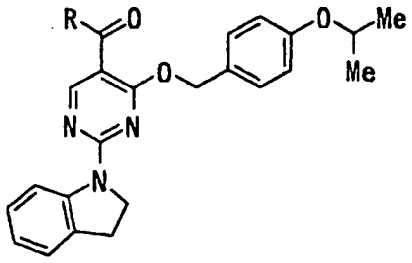
Example 29-4: N-(1H-benzimidazol-2-ylmethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-isopropoxybenzyl)oxy]-5-pyrimidinecarboxamide

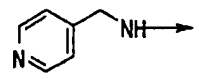
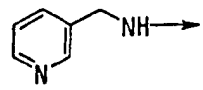
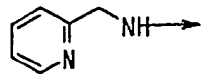
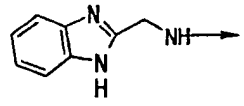
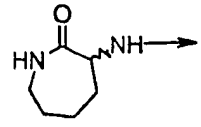
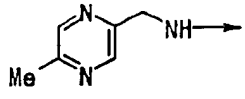
Example 29-5: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-isopropoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 29-6: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-isopropoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

[0288] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 64]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
29-1		51	496 $(M+H)^+$
29-2		61	496 $(M+H)^+$
29-3		65	496 $(M+H)^+$
29-4		22	535 $(M+H)^+$
29-5		47	516 $(M+H)^+$
29-6		55	511 $(M+H)^+$

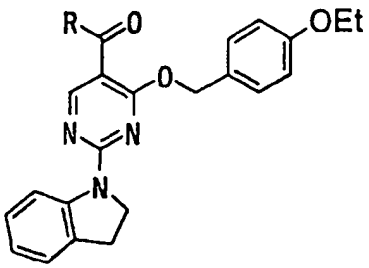
Example 30

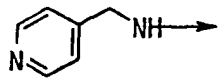
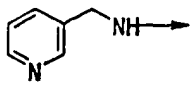
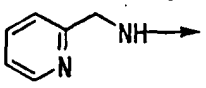
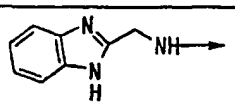
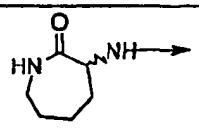
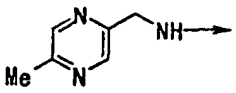
[0289] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-ethoxybenzyl)oxy]-5-py-

rimidinecarboxylate as a starting material, compounds of Examples 30-1 to 30-6 were synthesized.
Example 30-1: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-ethoxybenzyl)oxy]-N-(4-pyridinylmethyl)-5-pyrimidinecarboxamide
Example 30-2: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-ethoxybenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide
Example 30-3: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-ethoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide
Example 30-4: N-(1H-benzimidazol-2-ylmethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-ethoxybenzyl)oxy]-5-pyrimidinecarboxamide
Example 30-5: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-ethoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide
Example 30-6: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-ethoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

[0290] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 65]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
30-1		93	482 $(M+H)^+$
30-2		90	482 $(M+H)^+$
30-3		83	482 $(M+H)^+$
30-4		24	521 $(M+H)^+$
30-5		70	502 $(M+H)^+$
30-6		65	497 $(M+H)^+$

Example 31

[0291] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 31-1 to 31-8 were synthesized.
Example 31-1: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-(4-pyridinylmethyl)-5-pyrimidine-

carboxamide

Example 31-2: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 31-3: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 31-4: N-(1H-benzimidazol-2-ylmethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

Example 31-5: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

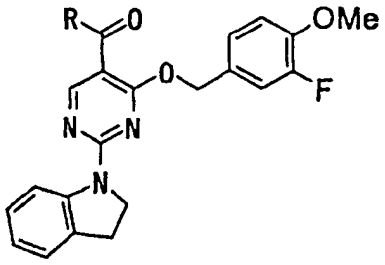
Example 31-6: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

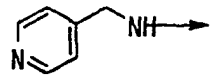
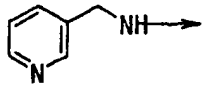
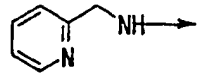
Example 31-7: N-cycloheptyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

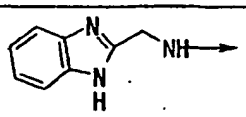
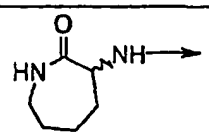
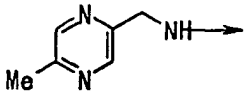
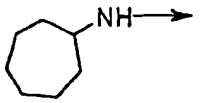
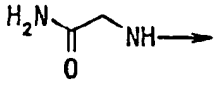
Example 31-8: N-(2-amino-2-oxoethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

[0292] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 66]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
31-1		75	486 $(M+H)^+$
31-2		79	486 $(M+H)^+$
31-3		73	486 $(M+H)^+$

31-4		80	525 (M+H)$^+$
31-5		93	506 (M+H)$^+$
31-6		77	501 (M+H)$^+$
31-7		42	491 (M+H)$^+$
31-8		48	452 (M+H)$^+$

Example 32

[0293] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxy-3-methylbenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 32-1 to 32-5 were synthesized.

Example 32-1: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxy-3-methylbenzyl)oxy]-N-(4-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 32-2: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxy-3-methylbenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

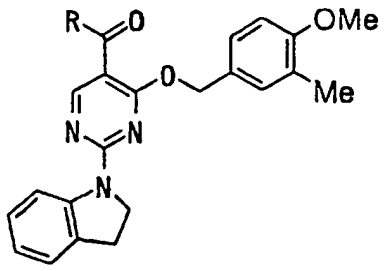
Example 32-3: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxy-3-methylbenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

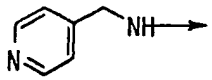
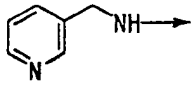
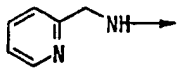
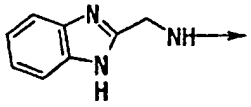
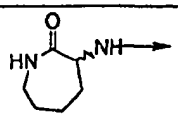
Example 32-4: N-(1H-benzimidazol-2-ylmethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxy-3-methylbenzyl)oxy]-5-pyrimidinecarboxamide

[0294] Example 32-5: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxy-3-methylbenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

[0295] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 67]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
32-1		35	482 $(M+H)^+$
32-2		61	482 $(M+H)^+$
32-3		47	482 $(M+H)^+$
32-4		56	497 $(M+H)^+$
32-5		45	502 $(M+H)^+$

Example 33

[0296] In the same manner as in Example 1-1 using ethyl 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 33-1 to 33-6 were synthesized.

Example 33-1: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(4-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 33-2: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 33-3: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

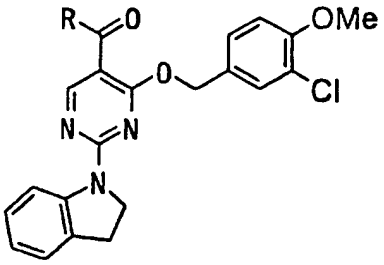
Example 33-4: N-(1H-benzimidazol-2-ylmethyl)-4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxamide

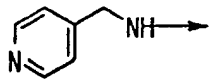
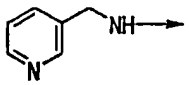
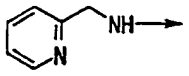
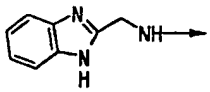
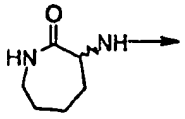
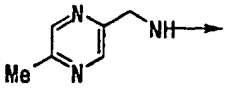
Example 33-5: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 33-6: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

[0297] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 68]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
33-1		22	502 $(M+H)^+$
33-2		54	502 $(M+H)^+$
33-3		58	502 $(M+H)^+$
33-4		43	656 $(M+H)^+$
33-5		53	522 $(M+H)^+$
33-6		76	516 $(M+H)^+$

Example 34

[0298] In the same manner as in Example 1-1 using ethyl 4-(2,3-dihydro-1-benzofuran-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 34-1 to 34-7 were synthesized.

Example 34-1: 4-(2,3-dihydro-1-benzofuran-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(4-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 34-2: 4-(2,3-dihydro-1-benzofuran-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 34-3: 4-(2,3-dihydro-1-benzofuran-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 34-4: N-(1H-benzimidazole-2-ylmethyl)-4-(2,3-dihydro-1-benzofuran-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxamide

Example 34-5: 4-(2,3-dihydro-1-benzofuran-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

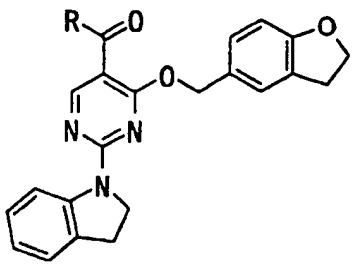
Example 34-6: 4-(2,3-dihydro-1-benzofuran-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

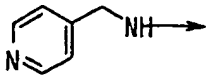
Example 34-7: N-(2-amino-2-oxoethyl)-4-(2,3-dihydro-1-benzofuran-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-5-py-

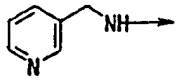
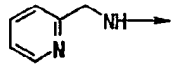
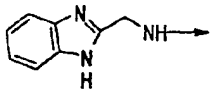
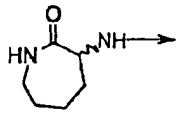
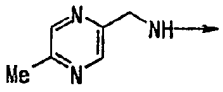
rimidinecarboxamide

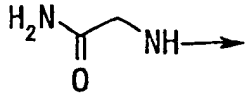
[0299] Respective structural formulas and NMR data are shown in the following Table.

[Table 69]



Example No.	R	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
34-1		28	3.10-3.30 (4H, m), 4.34 (2H, t, J=8.0 Hz), 4.52-4.65 (4H, m), 5.43 (2H, s), 6.75 (1H, d, J=7.6 Hz), 6.90-7.30 (7H, m), 7.70-7.80 (1H, br), 8.22-8.50 (3H, m), 9.15 (1H, s)

34-2		40	3.10-3.28 (4H, m), 4.34 (2H, t, J=8.2 Hz), 4.54-4.66 (4H, m), 5.46 (2H, s), 6.73 (1H, d, J=8.0 Hz), 6.95-7.25 (6H, m), 7.49 (1H, d, J=8.2 Hz), 7.73 (1H, t, J=7.0 Hz), 8.30-8.52 (3H, m), 9.15 (1H, s)
34-3		66	3.09-3.28 (4H, m), 4.34 (2H, t, J=8.4 Hz), 4.58 (2H, t, J=8.4 Hz), 4.72 (2H, d, J=4.8 Hz), 5.57 (2H, s), 6.75 (1H, d, J=8.0 Hz), 7.00 (1H, t, J=7.8 Hz), 7.10-7.36 (6H, m), 7.62 (1H, dt, J=1.8, 7.6 Hz), 8.30-8.50 (3H, m), 9.17 (1H, s)
34-4		56	3.03 (2H, t, J=8.4 Hz), 3.23 (2H, t, J=8.4 Hz), 4.33 (2H, t, J=8.8 Hz), 4.52 (2H, t, J=8.4 Hz), 4.80 (2H, d, J=5.4 Hz), 5.55 (2H, s), 6.67 (1H, d, J=5.4 Hz), 7.01 (1H, t, J=8.4 Hz), 7.18-7.31 (5H, m), 7,50-7.60 (2H, m)
34-5		43	1.40-2.24 (6H, m), 3.14-3.40 (6H, m), 4.32 (2H, t, J=8.4 Hz), 4.57 (2H, t, J=8.8 Hz), 4.68-4.80 (1H, m), 5.65 (2H, s), 5.88-6.00 (1H, m), 6.77 (1H, d, J=7.6 Hz), 7.00 (1H, t, J=6.8 Hz), 7.18-7.43 (4H, m), 8.39 (1H, d, J=8.8 Hz), 8.79 (1H, d, J=9.0 Hz), 9.09 (1H, s)
34-6		82	2.55 (3H, s), 3.10-3.29 (4H, m), 4.33 (2H, t, J=8.8 Hz), 4.60 (2H, t, J=8.4 Hz), 4.69 (2H, d, J=4.8 Hz), 5.53 (2H, s), 6.76 (1H, d, J=8.4 Hz), 7.00 (1H, t, J=7.0 Hz), 7.18-7.30 (4H, m), 8.15 (1H, s), 8.20-8.44 (3H, m), 9.15 (1H, s)

34-7		75	3.23 (4H, t, J=8.4 Hz), 4.08 (2H, d, J=5.4 Hz), 4.32 (2H, t, J=8.0 Hz), 4.59 (2H, t, J=8.4 Hz), 5.58 (2H, s), 5.70-5.88 (1H, br), 6.60-6.81 (2H, m), 7.00 (1H, t, J=7.6 Hz), 7.20-7.40 (3H, m), 8.06 (1H, br t, J=6.8 Hz), 8.37 (1H, d, J=8.0 Hz), 9.07 (1H, s)

Example 35

[0300] In the same manner as in Example 1-1 using ethyl 4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 35-1 to 35-6 were synthesized.

Example 35-1: t-butyl 2-({[4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino) acetate

Example 35-2: (RS)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

Example 35-3: (RS)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

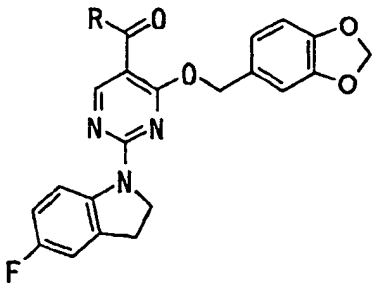
Example 35-4: 4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

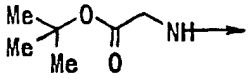
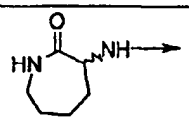
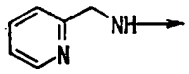
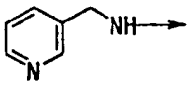
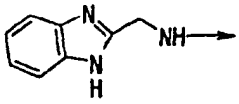
Example 35-5: 4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 35-6: N-(1H-benzimidazole-2-ylmethyl)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxamide

[0301] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 70]



Example No.	R	yield(%)	MASS spectrum (APCIMS, m/z)
35-1		80	523 $(M+H)^+$
35-2		53	593 $(M+H)^+$
35-3		81	520 $(M+H)^+$
35-4		68	500 $(M+H)^+$
35-5		65	500 $(M+H)^+$
35-6		71	539 $(M+H)^+$

Example 36

[0302] In the same manner as in Example 1-1 using ethyl 2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 36-1 to 36-5 were synthesized.

Example 36-1: t-butyl 2-[({2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinyl}carbonyl) amino]-acetate

Example 36-2: (RS)-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

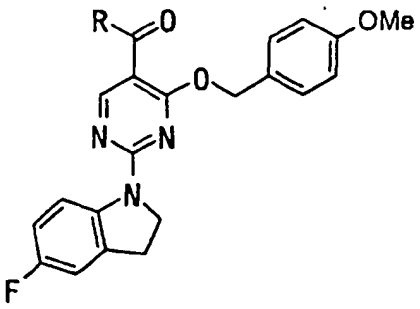
Example 36-3: (RS)-2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

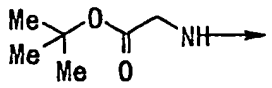
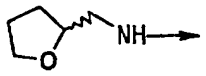
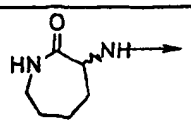
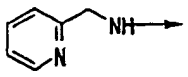
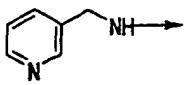
Example 36-4: 2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 36-5: 2-(5-fluoro-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

[0303] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 71]



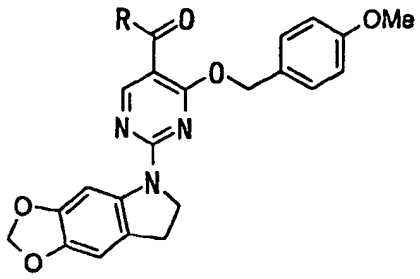
Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
36-1		93	509 $(M+H)^+$
36-2		60	479 $(M+H)^+$
36-3		84	506 $(M+H)^+$
36-4		74	486 $(M+H)^+$
36-5		62	486 $(M+H)^+$

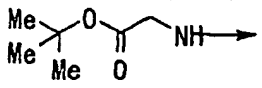
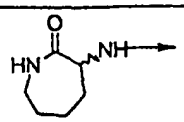
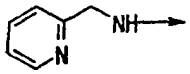
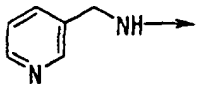
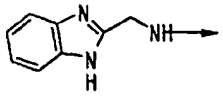
Example 37

[0304] In the same manner as in Example 1-1 using ethyl 2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 37-1 to 37-6 were synthesized.
Example 37-1: t-butyl 2-[({2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinyl)carbonyl)-amino]acetate
Example 37-2: (RS)-2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-methoxybenzyl)oxy]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide
Example 37-3: (RS)-2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide
Example 37-4: 2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide
Example 37-5: 2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-methoxybenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide
Example 37-6: N-(1H-benzimidazole-2-ylmethyl)-2-(6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

[0305] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 72]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
37-1		83	535 $(M+H)^+$
37-2		66	505 $(M+H)^+$
37-3		71	532 $(M+H)^+$
37-4		66	512 $(M+H)^+$
37-5		84	512 $(M+H)^+$
37-6		81	551 $(M+H)^+$

Example 38

[0306] In the same manner as in Example 1-1 using ethyl 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 38-1 to 38-6 were synthesized.

Example 38-1: t-butyl 2-[({2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinyl)carbonyl) amino]-acetate

Example 38-2: (RS)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

Example 38-3: (RS)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 38-4: 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-N-[2-(dimethylamino)ethyl]-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxamide

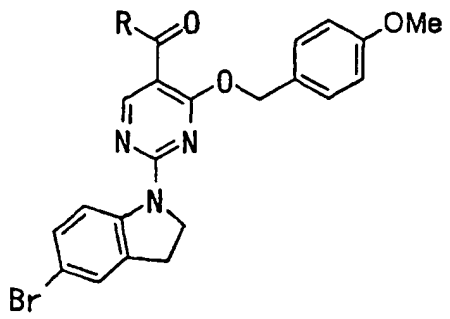
Example 38-5: 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

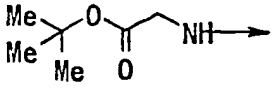
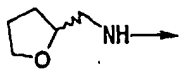
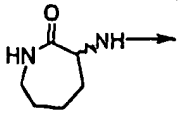
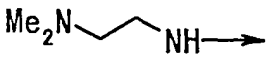
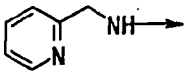
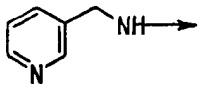
Example 38-6: 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(3-pyridinylmethyl)-5-pyrimidine-

carboxamide

[0307] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 73]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
38-1		79	570 $(M+H)^+$
38-2		80	540 $(M+H)^+$
38-3		55	567 $(M+H)^+$
38-4		86	527 $(M+H)^+$
38-5		89	547 $(M+H)^+$
38-6		54	547 $(M+H)^+$

Example 39

[0308] In the same manner as in Example 1-1 using ethyl 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 39-1 to 39-4 were synthesized.

Example 39-1: (RS)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

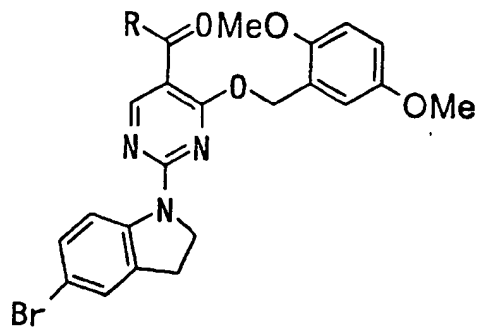
Example 39-2: t-butyl 3-[({2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]-propylcarbamate

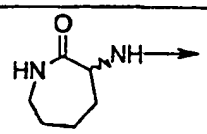
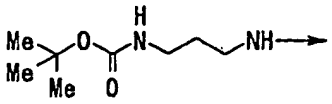
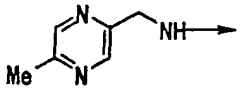
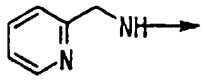
Example 39-3: 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 39-4: 2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-4-[(2,5-dimethoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0309] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 74]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
39-1		74	597 $(M+H)^+$
39-2		35	643 $(M+H)^+$
39-3		55	592 $(M+H)^+$
39-4		68	577 $(M+H)^+$

Example 40

[0310] In the same manner as in Example 1-1 using ethyl 4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 40-1 to 40-4 were synthesized.

Example 40-1: t-butyl 2-({[4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)acetate

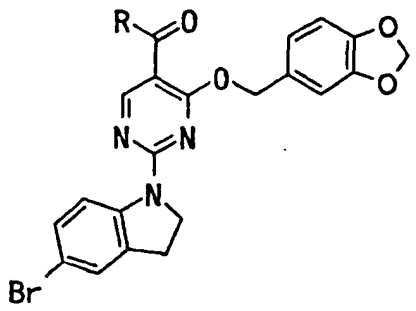
Example 40-2: (RS)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

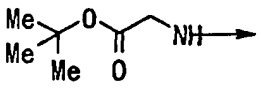
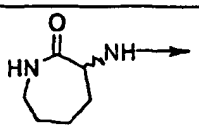
Example 40-3: (RS)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 40-4: 4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-bromo-2,3-dihydro-1H-indol-1-yl)-N-[2-(dimethylamino)ethyl]-5-pyrimidinecarboxamide

[0311] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 75]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
40-1		90	584 $(M+H)^+$
40-2		51	554 $(M+H)^+$
40-3		75	581 $(M+H)^+$
40-4		95	541 $(M+H)^+$

Example 41

[0312] In the same manner as in Example 1-1 using ethyl 4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 41-1 to 41-4 were synthesized.

Example 41-1: t-butyl 2-({[4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl] carbonyl}amino) acetate

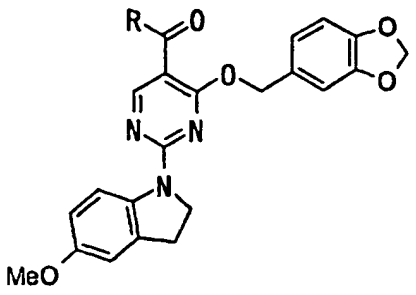
Example 41-2: (RS)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

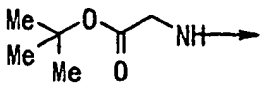
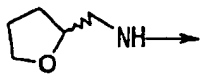
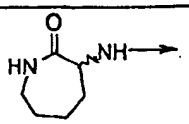
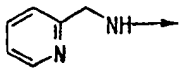
Example 41-3: (RS)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 41-4: 4-(1,3-benzodioxol-5-ylmethoxy)-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridylmethyl)-5-pyrimidinecarboxamide

[0313] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

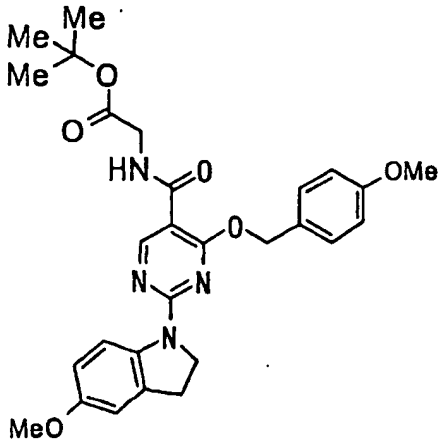
[Table 76]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
41-1		74	535(M+H)$^+$ 1.47 (9H, s), 3.20 (2H, t, J=8.4 Hz), 3.81 (3H, s), 4.08 (2H, d, J=4.8 Hz), 4.31 (2H, t, J=8.0 Hz), 5.55 (2H, s), 5.98 (2H, s), 6.85-6.94 (3H, m), 6.96-7.07 (2H, m), 7.91 (1H, t, J=7.0 Hz), 8.00-8.40 (1H, br), 9.09 (1H, s)
41-2		51	505(M+H)$^+$
41-3		68	532(M+H)$^+$
41-4		61	512(M+H)$^+$

Example 42

[0314] In the same manner as in Example 1-1 using ethyl 4-[(4-methoxybenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, t-butyl 2-({[4-[(4-methoxybenzyl)oxy]-2-(5-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)acetate was synthesized.



Yield 90%, MASS spectrum (APCIMS, m/z): 520

Example 43

[0315] In the same manner as in Example 1-1 using ethyl 4-[(2,5-dimethoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 43-1 to 43-4 were synthesized.

Example 43-1: (RS)-4-[(2,5-dimethoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

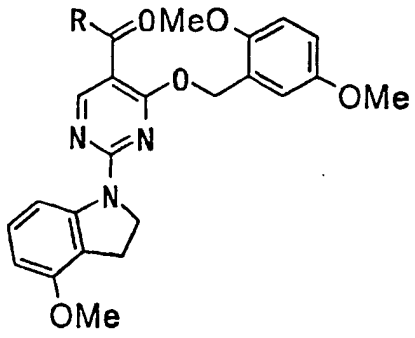
Example 43-2: t-butyl 3-({[4-[(2,5-dimethoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)propylcarbamate

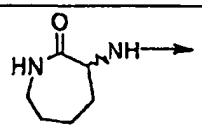
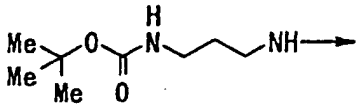
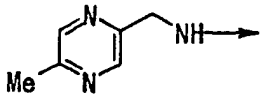
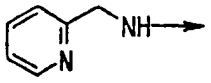
Example 43-3: 4-[(2,5-dimethoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 43-4: 4-[(2,5-dimethoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridylmethyl)-5-pyrimidinecarboxamide

[0316] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 77]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
43-1		35	548 (M+H)$^+$
43-2		82	594 (M+H)$^+$
43-3		75	543 (M+H)$^+$
43-4		62	528 (M+H)$^+$

Example 44

[0317] In the same manner as in Example 1-1 using ethyl 4-[(4-methoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 44-1 to 44-4 were synthesized.

Example 44-1: (RS)-4-[(4-methoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

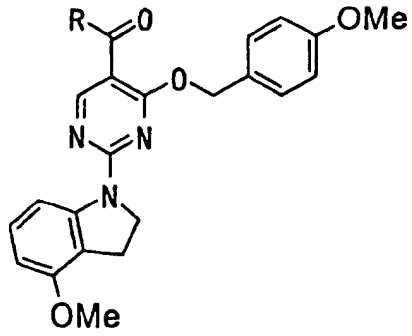
Example 44-2: t-butyl 3-({[4-[(4-methoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)propylcarbamate

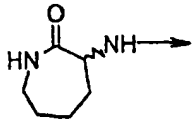
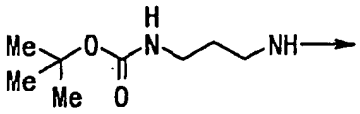
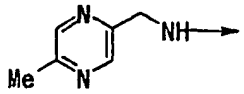
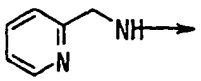
Example 44-3: 4-[(4-methoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 44-4: 4-[(4-methoxybenzyl)oxy]-2-(4-methoxy-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridylmethyl)-5-pyrimidinecarboxamide

[0318] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 78]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
44-1		56	518 $(M+H)^+$
44-2		80	564 $(M+H)^+$
44-3		75	513 $(M+H)^+$
44-4		61	498 $(M+H)^+$

Example 45

[0319] In the same manner as in Example 1-1 using ethyl 4-[(4-methoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 45-1 to 45-6 were synthesized.

Example 45-1: (RS)-4-[(4-methoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 45-2: t-butyl 3-({[4-[(4-methoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)propylcarbamate

Example 45-3: 4-[(4-methoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

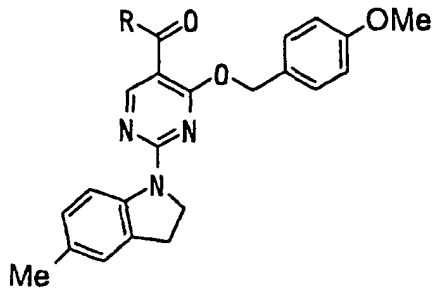
Example 45-4: 4-[(4-methoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

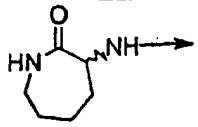
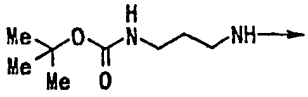
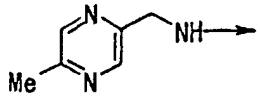
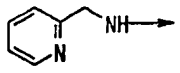
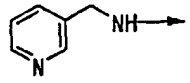
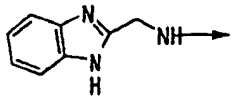
Example 45-5: 4-[(4-methoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 45-6: N-(1H-benzimidazole-2-ylmethyl)-4-[(4-methoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxamide

[0320] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 79]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
45-1		30	502 $(M+H)^+$
45-2		62	548 $(M+H)^+$
45-3		43	497 $(M+H)^+$ 2.33 (3H, s), 2.54 (3H, s), 3.18 (2H, t, J=8.8 Hz), 3.84 (3H, s), 4.31 (2H, t, J=8.4 Hz), 4.69 (2H, d, J=5.2 Hz), 5.54 (2H, s), 6.88 (2H, d, J=8.8 Hz), 7.00-7.08 (2H, m), 7.40 (2H, d, J=8.4 Hz), 8.13-8.32 (3H, m), 8.44 (1H, s), 9.13 (1H, s)
45-4		62	482 $(M+H)^+$
45-5		83	482 $(M+H)^+$
45-6		57	521 $(M+H)^+$

Example 46

[0321] In the same manner as in Example 1-1 using ethyl 4-[(2,5-dimethoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 46-1 to 46-4 were synthesized.

Example 46-1: (RS)-4-[(2,5-dimethoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

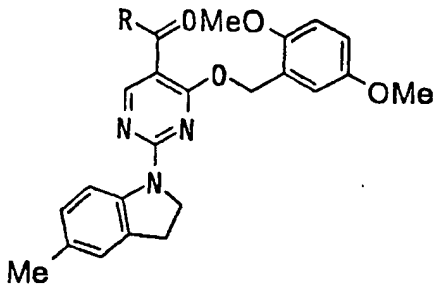
Example 46-2: t-butyl 3-({[4-[(2,5-dimethoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)propylcarbamate

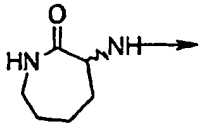
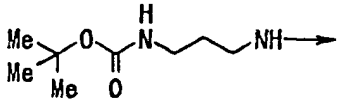
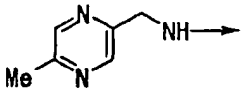
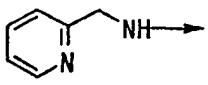
Example 46-3: 4-[(2,5-dimethoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide

Example 46-4: 4-[(2,5-dimethoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0322] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 80]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
46-1		30	532 $(M+H)^+$
46-2		73	578 $(M+H)^+$
46-3		77	527 $(M+H)^+$
46-4		83	512 $(M+H)^+$

Example 47

[0323] In the same manner as in Example 1-1 using ethyl (RS)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 47-1 to 47-3 were synthesized.

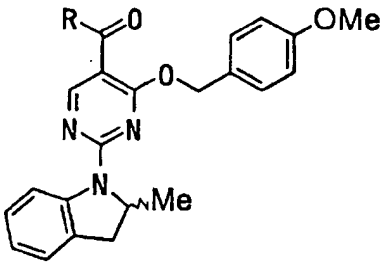
Example 47-1: t-butyl (RS)-2-({[4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)acetate

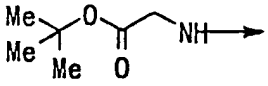
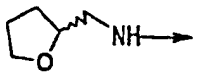
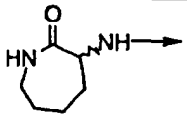
Example 47-2: (rac)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide

Example 47-3: (rac)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

[0324] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 81]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
47-1		80	505 $(M+H)^+$
47-2		82	475 $(M+H)^+$
47-3		65	502 $(M+H)^+$

Example 48

[0325] In the same manner as in Example 1-1 using ethyl (RS)-4-[(4-methoxybenzyl)oxy]-2-(3-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 48-1 to 48-3 were synthesized.

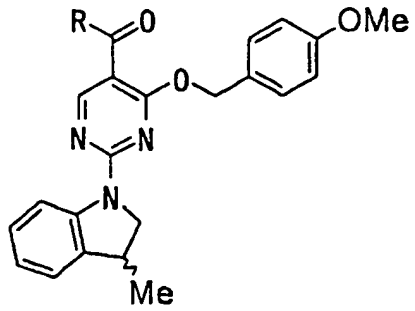
Example 48-1: (RS)-4-[(4-methoxybenzyl)oxy]-2-(3-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

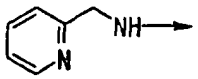
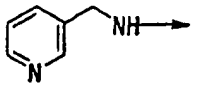
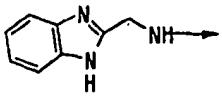
Example 48-2: (RS)-4-[(4-methoxybenzyl)oxy]-2-(3-methyl-2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide

Example 48-3: (RS)-N-(1H-benzimidazole-2-ylmethyl)-4-[(4-methoxybenzyl)oxy]-2-(3-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxamide

[0326] Respective structural formulas and MASS spectrum data are shown in the following Table.

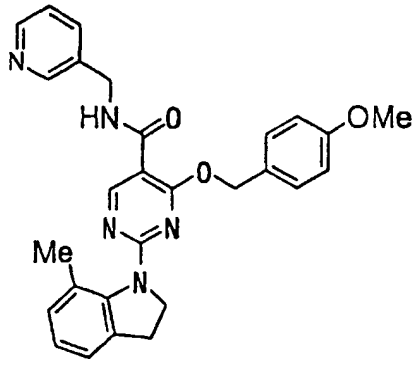
[Table 82]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
48-1		88	482 $(M+H)^+$
48-2		35	482 $(M+H)^+$
48-3		48	521 $(M+H)^+$

Example 49

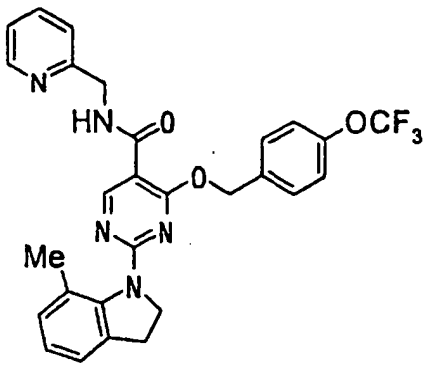
[0327] In the same manner as in Example 1-1 using ethyl 4-[(4-methoxybenzyl)oxy]-2-(7-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, 4-[(4-methoxybenzyl)oxy]-2-(7-methyl-2,3-dihydro-1H-indol-1-yl)-N-(3-pyridinylmethyl)-5-pyrimidinecarboxamide was synthesized.



Yield 25%, MASS spectrum (APCIMS, m/z): 482

Example 50

[0328] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoromethoxy)benzyl]oxy)-5-pyrimidinecarboxylate as a starting material, 2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-4-{[4-(trifluoromethoxy)-benzyl]oxy}-5-pyrimidinecarboxamide was synthesized.



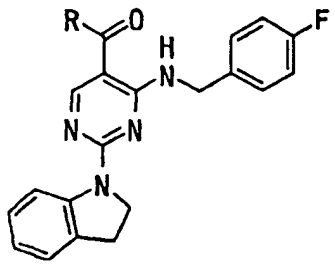
Yield 48%, MASS spectrum (APCIMS, m/z): 522

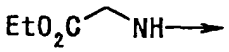
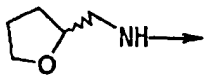
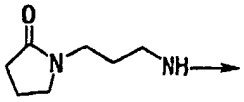
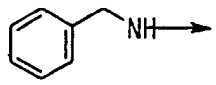
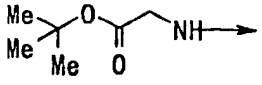
Example 51

[0329] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)amino]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 51-1 to 51-6 were synthesized.
Example 51-1: N-(cyanomethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)amino]-5-pyrimidinecarboxamide
Example 51-2: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate
Example 51-3: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)amino]-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide
Example 51-4: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)amino]-N-[3-(2-oxo-1-pyrrolizinyl)propyl]-5-pyrimidinecarboxamide
Example 51-5: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)amino]-5-pyrimidinecarboxamide
Example 51-6: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

[0330] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 83]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
51-1		35	403 $(M+H)^+$
51-2		32	450 $(M+H)^+$
51-3		35	448 $(M+H)^+$
51-4		25	489 $(M+H)^+$ 1.20-1.90 (5H, m), 2.07 (3H, t, J=7.6 Hz), 2.45 (2H, t, J=8.0 Hz), 3.13 (2H, t, J=8.8 Hz), 3.21-3.50 (4H, m), 4.21 (2H, t, J=8.8 Hz), 4.71 (2H, d, J=5.4 Hz), 6.80-7.42 (6H, m), 7.70 (1H, br t, J=7.4 Hz), 8.24 (1H, dd, J=8.0 Hz), 8.60 (1H, s), 9.23 (1H, br s)
51-5		34	454 $(M+H)^+$
51-6		60	478 $(M+H)^+$

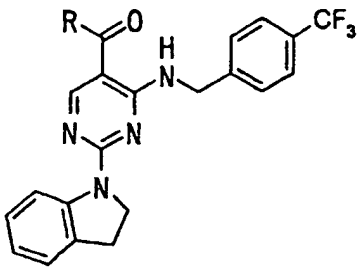
Example 52

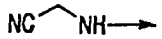
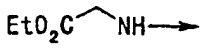
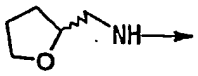
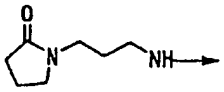
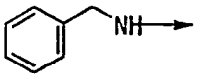
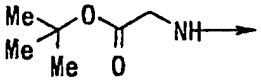
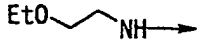
[0331] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoro)benzyl]amino}-5-pyrimidinecarboxylate as a starting material, compounds of Examples 51-1 to 52-7 were synthesized.

Example 52-1: N-(cyanomethyl)-2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoro)benzyl]amino}-5-pyrimidinecarboxamide
Example 52-2: ethyl 2-{[(2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoro)benzyl]amino)-5-pyrimidinyl)carbonyl]amino)acetate
Example 52-3: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoro)benzyl]amino)-N-(tetrahydro-2-furanylmethyl)-5-pyrimidinecarboxamide
Example 52-4: 2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoro)benzyl]amino)-N-[3-(2-oxo-1-pyrrolizinyl)propyl]-5-pyrimidinecarboxamide
Example 52-5: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoro)benzyl]amino}-5-pyrimidinecarboxamide
Example 52-6: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-{[4-(trifluoro)benzyl]amino)-5-pyrimidinyl}carbonyl)amino]acetate
Example 52-7: 2-(2,3-dihydro-1H-indol-1-yl)-N-(2-ethoxyethyl)-4-{[4-(trifluoro)benzyl]amino}-5-pyrimidinecarboxamide

[0332] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 84]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
52-1		35	453 $(M+H)^+$
52-2		28	500 $(M+H)^+$
52-3		30	498 $(M+H)^+$
52-4		25	539 $(M+H)^+$
52-5		45	504 $(M+H)^+$ 3.13 (2H, t, J=8.0 Hz), 4.17 (2H, t, J=8.4 Hz), 4.60 (2H, d, J=5.4 Hz), 4.82 (2H, d, J=5.4 Hz), 6.25 (1H, t, J=7.0 Hz), 6.91 (1H, t, J=7.2 Hz), 7.00-7.40 (4H, m), 7.50 (2H, d, J=8.8 Hz), 7.59 (2H, d, J=8.8 Hz), 8.00-8.23 (1H, br), 8.35 (1H, s), 9.24 (1H, br t, J=7.0 Hz)
52-6		15	528 $(M+H)^+$
52-7		16	486 $(M+H)^+$

Example 53

[0333] In the same manner as in Example 1-1 using ethyl 4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 53-1 to 53-3 were synthesized.

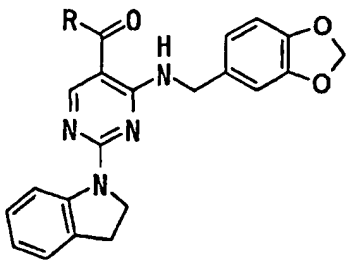
Example 53-1: 4-[(1,3-benzodioxol-5-ylmethyl)amino]-N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxamide

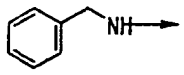
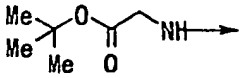
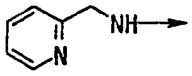
Example 53-2: t-butyl 2-({[4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl)amino)acetate

Example 53-3: 4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0334] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 85]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
53-1		71	480 $(M+H)^+$
53-2		39	504 $(M+H)^+$
53-3		35	481 $(M+H)^+$

Example 54

[0335] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-phenylpropyl)amino]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 54-1 to 54-4 were synthesized.

Example 54-1: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-phenylpropyl)amino]-5-pyrimidinyl)carbonyl)amino]acetate

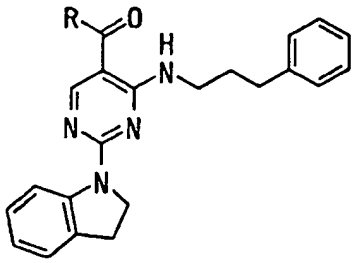
Example 54-2: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-phenylpropyl)amino]-5-pyrimidinecarboxamide

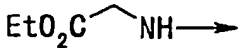
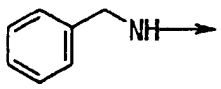
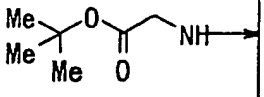
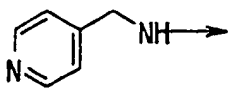
Example 54-3: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-phenylpropyl)amino]-5-pyrimidinyl)carbonyl)amino]acetate

Example 54-4: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-phenylpropyl)amino]-N-(4-pyridinylmethyl)-5-pyrimidinecarboxamide

[0336] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 86]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
54-1		78	460 $(M+H)^+$
54-2		69	464 $(M+H)^+$
54-3		55	488 $(M+H)^+$
54-4		20	465 $(M+H)^+$

Example 55

[0337] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxyphenethyl)amino]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 55-1 to 55-4 were synthesized.

Example 55-1: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxyphenethyl)amino]-5-pyrimidinyl}carbonyl)amino] acetate

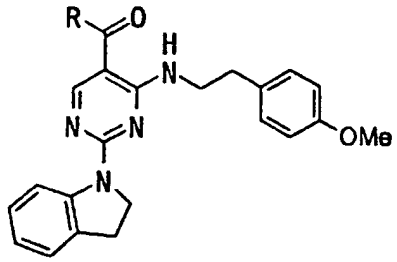
Example 55-2: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxyphenethyl)amino]-5-pyrimidinecarboxamide

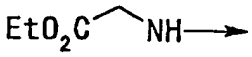
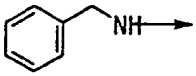
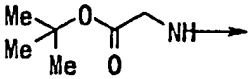
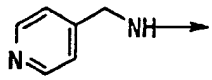
Example 55-3: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxyphenethyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

Example 55-4: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxyphenethyl)amino]-N-(4-pyridinylmethyl)-5-pyrimidinecarboxamide

[0338] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 87]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
55-1		73	476 $(M+H)^+$
55-2		49	480 $(M+H)^+$
55-3		69	504 $(M+H)^+$
55-4		24	481 $(M+H)^+$

Example 56

[0339] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-thienylmethyl)amino]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 56-1 to 56-4 were synthesized.

Example 56-1: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-thienylmethyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

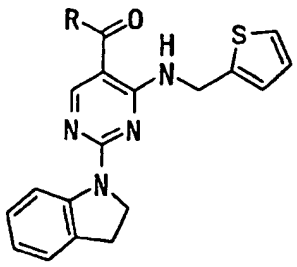
Example 56-2: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-thienylmethyl)amino]-5-pyrimidinecarboxamide

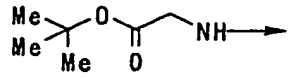
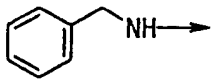
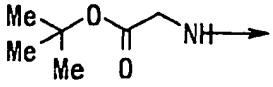
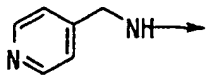
Example 56-3: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-thienylmethyl)amino]-5-pyrimidinyl)carbonyl)amino]acetate

Example 56-4: 2-(2,3-dihydro-1H-indol-1-yl)-N-(4-pyridinylmethyl)-4-[(2-thienylmethyl)amino]-5-pyrimidinecarboxamide

[0340] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 88]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
56-1		41	438(M+H)$^+$
56-2		45	442(M+H)$^+$ 3.17 (2H, t, J=9.2 Hz), 4.28 (2H, t, J=8.8 Hz), 4.58 (2H, d, J=5.6 Hz), 4.93 (2H, d, J=5.4 Hz), 6.20 (1H, br t, J=7.0 Hz), 6.90-7.08 (3H, m), 7.10-7.40 (7H, m), 8.31-8.39 (2H, m), 9.00-9.10 (1H, br)
56-3		49	466(M+H)$^+$
56-4		38	443(M+H)$^+$

Example 57

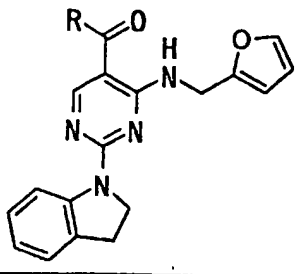
[0341] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-furylmethyl)amino]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 57-1, 56-2 were synthesized.

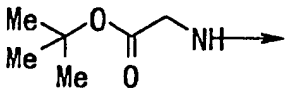
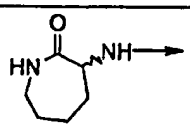
Example 57-1: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-furylmethyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

Example 57-2: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-furylmethyl)amino]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

[0342] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 89]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
57-1		50	450 $(M+H)^+$
57-2		32	447 $(M+H)^+$

Example 58

[0343] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluorobenzyl)amino]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 58-1 to 58-6 were synthesized.

Example 58-1: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluorobenzyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

Example 58-2: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluorobenzyl)amino]-5-pyrimidinecarboxamide

Example 58-3: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluorobenzyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

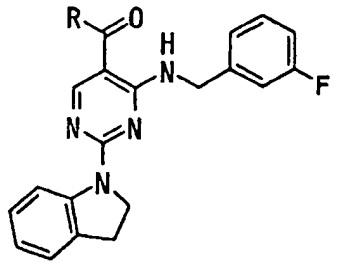
Example 58-4: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluorobenzyl)amino]-N-(4-pyridinylmethyl)-5-pyrimidinecarboxamide

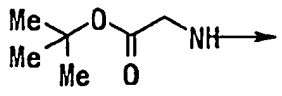
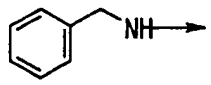
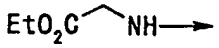
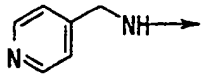
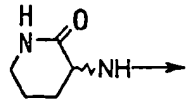
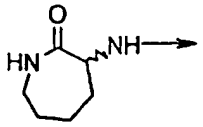
Example 58-5: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluorobenzyl)amino]-N-(2-oxo-3-piperidinyl)-5-pyrimidinecarboxamide

Example 58-6: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluorobenzyl)amino]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

[0344] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 90]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
58-1		70	478 $(M+H)^+$
58-2		32	454 $(M+H)^+$
58-3		25	450 $(M+H)^+$
58-4		18	455 $(M+H)^+$
58-5		26	461 $(M+H)^+$
58-6		5	475 $(M+H)^+$

Example 59

[0345] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)amino]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 59-1 to 59-6 were synthesized.

Example 59-1: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

Example 59-2: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)amino]-5-pyrimidinecarboxamide

Example 59-3: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)amino] -5-pyrimidinyl}carbonyl)amino]acetate

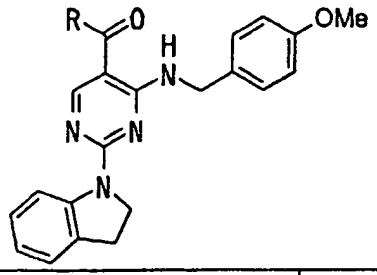
Example 59-4: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)amino]-N-(4-pyridinylmethyl)-5-pyrimidinecarboxamide

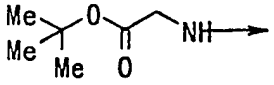
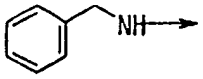
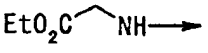
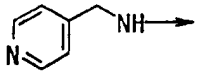
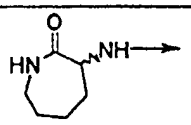
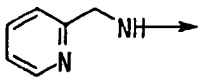
Example 59-5: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)amino]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

Example 59-6: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)amino]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

[0346] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 91]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
59-1		70	490 $(M+H)^+$
59-2		28	466 $(M+H)^+$
59-3		62	462 $(M+H)^+$
59-4		12	467 $(M+H)^+$
59-5		25	487 $(M+H)^+$
59-6		72	479 $(M+H)^+$

Example 60

[0347] In the same manner as in Example 1-1 using ethyl 4-[(2,6-difluorobenzyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, compounds of Examples 60-1 to 60-6 were synthesized.

Example 60-1: t-butyl 2-({[4-[(2,6-difluorobenzyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)-acetate

Example 60-2: N-benzyl-4-[(2,6-difluorobenzyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxamide

Example 60-3: ethyl 2-({[4-[(2,6-difluorobenzyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinyl]carbonyl}amino)acetate

Example 60-4: 4-[(2,6-difluorobenzyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-N-(4-pyridinylmethyl)-5-pyrimidinecarboxamide

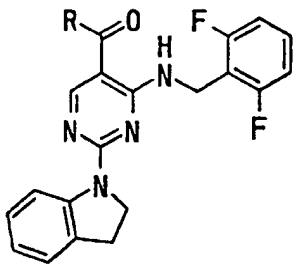
Example 60-5: (RS)-4-[(2,6-difluorobenzyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

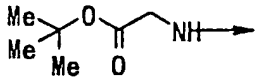
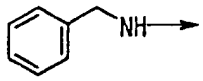
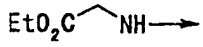
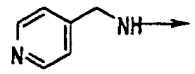
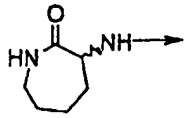
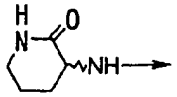
Example 60-6: (RS)-4-[(2,6-difluorobenzyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-piperidinyl)-5-pyrimidine-

carboxamide

[0348] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 92]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
60-1		53	496 $(M+H)^+$
60-2		18	472 $(M+H)^+$
60-3		52	468 $(M+H)^+$
60-4		13	473 $(M+H)^+$
60-5		25	493 $(M+H)^+$
60-6		10	479 $(M+H)^+$

Example 61

[0349] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methylbenzyl)amino]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 61-1 to 61-4 were synthesized.

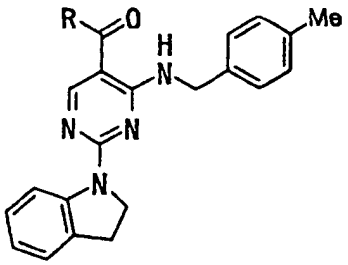
Example 61-1: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methylbenzyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

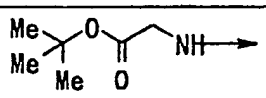
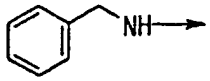
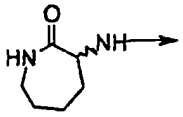
Example 61-2: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methylbenzyl)amino]-5-pyrimidinecarboxamide

Example 61-3: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methylbenzyl)amino]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide

[0350] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 93]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
61-1		80	474 $(M+H)^+$
61-2		15	450 $(M+H)^+$
61-3		7	471 $(M+H)^+$

Example 62

[0351] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-pyridinylmethyl)amino]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 62-1 to 62-4 were synthesized.

Example 62-1: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-pyridinylmethyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

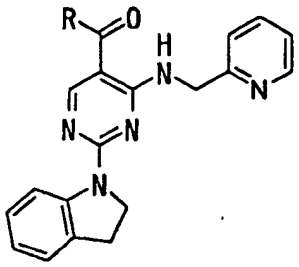
Example 62-2: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-pyridinylmethyl)amino]-5-pyrimidinecarboxamide

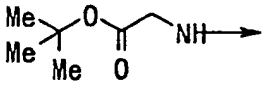
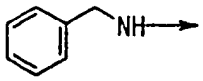
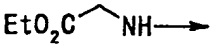
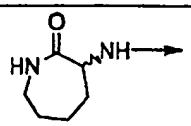
Example 62-3: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(2-pyridinylmethyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

Example 62-4: (RS)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-4-[(2-pyridinylmethyl)amino]-5-pyrimidinecarboxamide

[0352] Respective structural formulas and MASS spectrum data are shown in the following Table.

[Table 94]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
62-1		48	461 $(M+H)^+$
62-2		45	437 $(M+H)^+$
62-3		32	433 $(M+H)^+$
62-4		5	458 $(M+H)^+$

Example 63

[0353] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-pyridinylmethyl)amino]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 63-1 to 63-4 were synthesized.

Example 63-1: t-butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-pyridinylmethyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

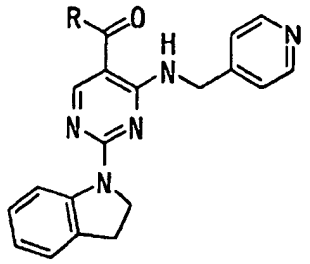
Example 63-2: N-benzyl-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-pyridinylmethyl)amino]-5-pyrimidinecarboxamide

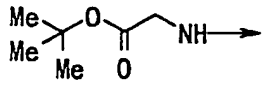
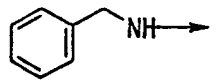
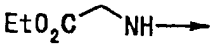
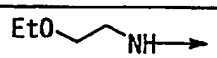
Example 63-3: ethyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-pyridinylmethyl)amino]-5-pyrimidinyl}carbonyl)amino]acetate

Example 63-4: 2-(2,3-dihydro-1H-indol-1-yl)-N-(ethoxyethyl)-4-[(4-pyridinylmethyl)amino]-5-pyrimidinecarboxamide

[0354] Respective structural formulas and MASS spectrum data are shown in the following Table.

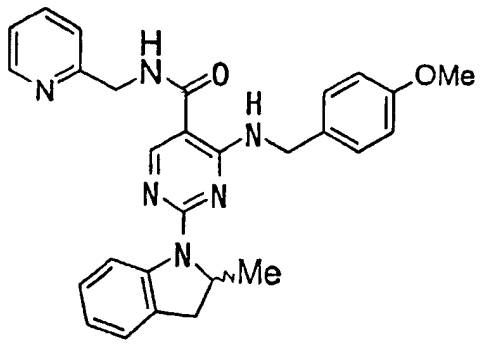
[Table 95]



Example No.	R	yield (%)	MASS spectrum (APCIMS, m/z)
63-1		53	461 $(M+H)^+$
63-2		62	437 $(M+H)^+$
63-3		78	433 $(M+H)^+$
63-4		45	419 $(M+H)^+$

Example 64

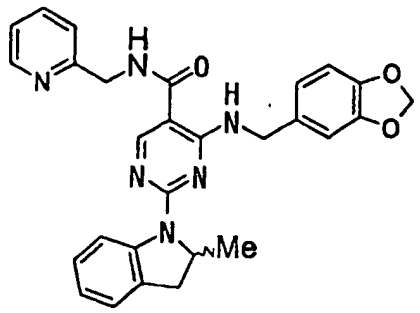
[0355] In the same manner as in Example 1-1 using ethyl (RS)-4-[(4-methoxybenzyl)amino]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, (RS)-4-[(4-methoxybenzyl)amino]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide was synthesized.



Yield 71%, MASS spectrum (APCIMS, m/z): 481

Example 65

[0356] In the same manner as in Example 1-1 using ethyl (RS)-4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate as a starting material, (RS)-4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide was synthesized.



Yield 38%, MASS spectrum (APCIMS, m/z): 495

Example 66-1

2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

[0357] To a suspension of ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate (5.5 g, 13.6 mmol) in ethanol (50 mL) were added 10% aqueous sodium hydroxide solution (30 mL) and tetrahydrofuran (30 mL) and the mixture was heated under reflux for 30 min. The reaction mixture was allowed to cool to room temperature and 1N hydrochloric acid was added to adjust the reaction mixture to pH 5. The precipitated crystals were collected by filtration, washed several times with water, and dried with heating under vacuum to give 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxylic acid (4.9 g, 96%) as crystals. A suspension of the obtained carboxylic acid (564 mg, 1.5 mmol), L-α-amino-ε-caprolactam (384 mg, 3.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (612 mg, 3.0 mmol) and 1-hydroxybenzotriazole (408 mg, 3.0 mmol) in dichloromethane (2 mL) was stirred at room temperature for 18 h. Water and ethyl acetate were added to the reaction mixture and the organic layer was concentrated under reduced pressure. The obtained residue was subjected to silica gel chromatography and eluted with ethyl acetate to give the title compound (650 mg, 89%).

[0358] In the same manner as in Example 66-1, compounds of Examples 66-2 to 66-25 were synthesized from ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate, ethyl 4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-isopropoxybenzyl)oxy]-5-pyrimidinecarboxylate, ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-ethoxybenzyl)oxy]-5-pyrimidinecarboxylate, ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-5-pyrimidinecarboxylate, ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxy-3-methylbenzyl)oxy]-5-pyrimidinecarboxylate, ethyl 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl 4-(2,3-dihydro-1-benzofuran-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl 4-[(4-methoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl (RS)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl (RS)-4-[(4-methoxybenzyl)oxy]-2-(3-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl (R)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl (R)-4-[(3-fluoro-4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl (R)-4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl (R)-4-[(2-fluoro-4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl (R)-4-[(2-chloro-4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl (S)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl 4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate, ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)amino]-5-pyrimidinecarboxylate, ethyl (RS)-4-[(4-methoxybenzyl)amino]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-5-pyrimidinecarboxylate and ethyl (RS)-4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl) -5-pyrimidinecarboxylate.

Example 66-2: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-3: 4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-4: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-isopropoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-5: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-ethoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-6: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-7: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxy-3-methylbenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-8: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-9: 4-(2,3-dihydro-1-benzofuran-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-10: 4-[(4-methoxybenzyl)oxy]-2-(5-methyl-2,3-dihydro-1H-indol-1-yl)-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-11: 4-[(4-methoxybenzyl)oxy]-2-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-12: 4-[(4-methoxybenzyl)oxy]-2-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-13: 4-[(4-methoxybenzyl)oxy]-2-[(3RS)-3-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-14: 4-[(4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-15: 4-[(4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-16: 2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-17: 4-[(3-chloro-4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-18: 2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-4-[(2-fluoro-4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-19: 4-[(2-chloro-4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-20: 4-[(4-methoxybenzyl)oxy]-2-[(2S)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-21: 4-[(4-methoxybenzyl)oxy]-2-[(2S)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide

Example 66-22: 4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)amino]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

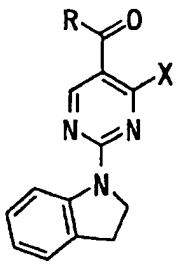
Example 66-23: 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)amino]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

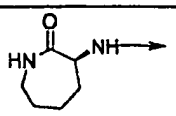
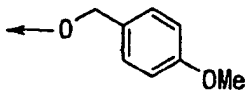
Example 66-24: 4-[(4-methoxybenzyl)amino]-2-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

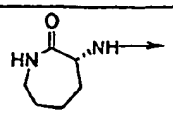
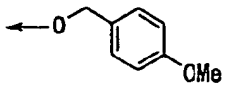
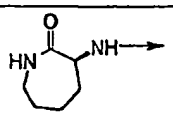
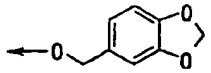
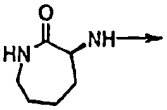
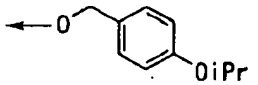
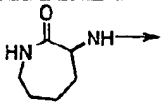
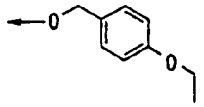
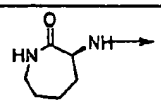
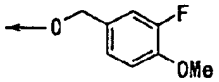
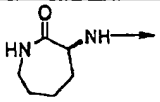
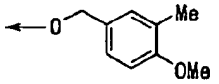
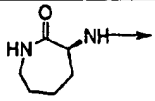
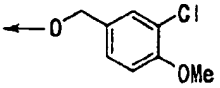
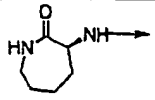
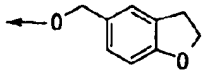
Example 66-25: 4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-4-[(4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

[0359] Respective structural formulas, MASS spectrum data and NMR data are shown in the following Table.

[Table 96]

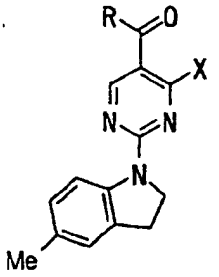


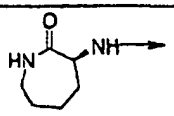
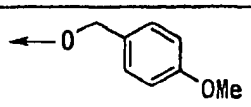
Example No.	R	X	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
66-1			43	488 $(M+H)^+$

66-2			29	488 (M+H)$^+$
66-3			90	502 (M+H)$^+$
66-4			62	516 (M+H)$^+$
66-5			96	502 (M+H)$^+$ 1.20-1.63 (5H, m), 1.70-2.24 (4H, m), 3.17-3.40 (4H, m), 4.02 (2H, q, J=7.0 Hz), 4.31 (2H, t, J=8.0 Hz), 4.68-4.80 (1H, m), 5.67 (2H, s), 5.91 (1H, br s), 6.82-7.03 (3H, m), 7.17-7.30 (2H, m), 7.50 (2H, d, J=8.4 Hz), 8.36 (1H, br s), 8.80 (1H, br d, J=6.8 Hz), 9.08 (1H, s)
66-6			70	506 (M+H)$^+$
66-7			50	502 (M+H)$^+$
66-8			34	522 (M+H)$^+$
66-9			63	500 (M+H)$^+$ 1.15-2.23 (6H, m), 3.14-3.32 (6H, m), 4.32 (2H, t, J=8.4 Hz), 4.57 (2H,

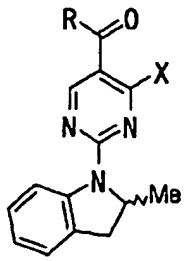
				t, J=8.8 Hz), 4.70-4.80 (1H, m), 5.65 (2H, s), 5.89 (1H, br t, J=7.0 Hz), 6.77 (1H, d, J=8.0 Hz), 7.00 (1H, t, J=6.2 Hz), 7.20-7.38 (2H, m), 7.43 (1H, br s), 8.40 (1H, br d, J=7.0 Hz), 8.78 (1H, br d, J=7.0 Hz), 9.09 (1H, s)

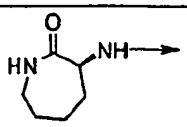
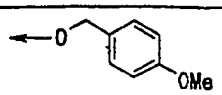
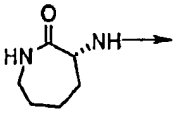
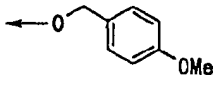
[Table 97]



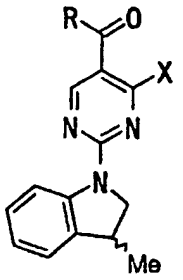
Example No.	R	X	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
66-10			61	502 $(M+H)^+$

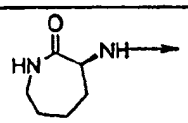
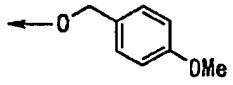
[Table 98]



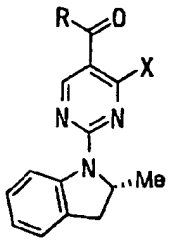
Example No.	R	X	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
66-11			50	502(M+H)$^+$ 1.30-1.62 (5H, m), 1.70-2.24 (4H, m), 2.71 (1H, d, J=16.2 Hz), 3.20-3.50 (3H, m), 3.79 (3H, s), 4.78 (1H, dd, J=6.2, 9.8 Hz), 5.02 (1H, quintet, J=8.0 Hz), 5.65 (2H, s), 6.24 (1H, br t, J=7.0 Hz), 6.82-7.03 (3H, m), 7.18-7.30 (2H, m), 7.50 (2H, d, J=8.8 Hz), 8.31 (1H, d, J=8.8 Hz), 8.77 (1H, d, J=4.8 Hz), 9.07 (1H, s)
66-12			92	502(M+H)$^+$

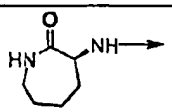
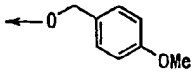
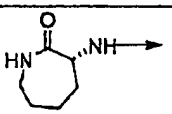
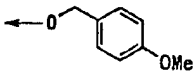
[Table 99]

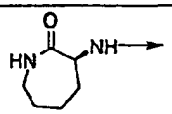
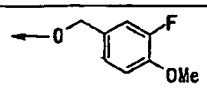
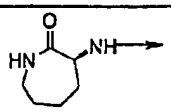
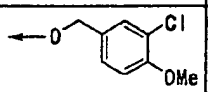
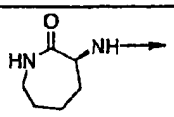
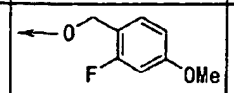


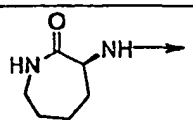
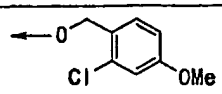
Example No.	R	X	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
66-13			40	502 $(M+H)^+$

[Table 100]

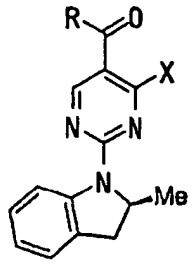


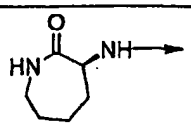
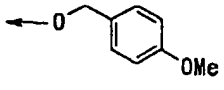
Example No.	R	X	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
66-14			75	502(M+H)$^+$ 1.30-1.60 (5H, m), 1.70-2.24 (4H, m), 2.71 (1H, d, J=15.8 Hz), 3.22-3.50 (3H, m), 3.80 (3H, s), 4.74 (1H, dd, J=6.4, 10.0 Hz), 5.03 (1H, quintet, J=8.0 Hz), 5.66 (2H, s), 5.90-6.02 (1H br), 6.84-7.04 (3H, m), 7.20-7.30 (2H, m), 7.50 (2H, d, J=8.4 Hz), 8.32 (1H, d, J=7.6 Hz), 8.77 (1H, d, J=6.6 Hz), 9.08 (1H, s)
66-15			55	502(M+H)$^+$ 1.30-1.70 (5H, m), 1.73-2.23 (4H, m), 2.71 (1H, d, J=16.8 Hz), 3.22-3.50 (3H, m), 3.80 (3H, s), 4.75 (1H, dd, J=5.8, 9.4 Hz), 4.90-5.08 (1H, m), 5.65 (2H, s), 5.95 (1H, br t, J=7.0 Hz), 6.88-7.05 (3H, m), 7.18-7.30 (2H, m), 7.50 (2H, d, J=8.6 Hz), 8.32 (1H, d, J=7.6 Hz), 8.77 (1H, d, J=5.6 Hz), 9.07 (1H, s)

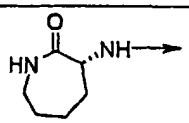
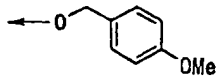
66-16			77	1.34 (3H, d, J=6.6 Hz), 1.40-1.70 (3H, m), 1.80-2.28 (4H, m), 2.72 (1H, d, J=16.0 Hz), 3.22-3.50 (3H, m), 3.80 (3H, s), 4.75 (1H, dd, J=6.0, 11.4 Hz), 5.02 (1H, quintet, J=7.0 Hz), 5.63 (2H, s), 5.91 (1H, t, J=6.0 Hz), 6.90-7.08 (2H, m), 7.19-7.37 (4H, m), 8.28 (1H, d, J=7.0 Hz), 8.76 (1H, d, J=5.0 Hz), 9.08 (1H, s)
66-17			79	1.35 (3H, d, J=6.2 Hz), 1.40-1.70 (3H, m), 1.80-2.27 (4H, m), 2.72 (1H, d, J=14.6 Hz), 3.25-3.50 (3H, m), 3.89 (3H, s), 4.75 (1H, dd, J=6.0, 10.0 Hz), 5.00 (1H, quintet, J=7.0 Hz), 5.62 (2H, s), 5.91 (1H, t, J=6.0 Hz), 6.90-7.07 (2H, m), 7.19-7.29 (3H, m), 7.45 (1H, dd, J=2.2, 8.4 Hz), 7.58 (1H, d, J=2.2 Hz), 8.27 (1H, d, J=6.6 Hz), 8.75 (1H, d, J=5.8 Hz), 9.08 (1H, s)
66-18			80	1.30-2.23 (10H, m), 2.71 (1H, d, J=15.8 Hz), 3.20-3.50 (3H, m), 3.80 (3H, s), 4.75 (1H, dd, J=6.6, 11.2 Hz), 4.96-5.13 (1H, m), 5.70 (2H, ABq), 5.90 (1H, t,

				J=7.0 Hz), 6.63-6.76 (2H, m), 7.01 (1H, t, J=7.4 Hz), 7.20-7.30 (2H, m), 7.50 (1H, t, J=8.4 Hz), 8.32 (1H, d, J=7.8 Hz), 8.70 (1H, d, J=6.2 Hz), 9.08 (1H, s)
66-19			79	1.28-1.70 (6H, m), 1.71-2.26 (4H, m), 2.70 (1H, d, J=16.6 Hz), 3.21-3.49 (3H, m), 3.80 (3H, s), 4.77 (1H, dd, J=6.4, 9.6 Hz), 4.95-5.10 (1H, m), 5.75 (2H, ABq), 5.86 (1H, t, J=7.0 Hz), 6.82 (1H, dd, J=2.6, 8.4 Hz), 6.94-7.04 (2H, m), 7.17-7.28 (2H, m), 7.49 (1H, d, J=8.8 Hz), 8.24 (1H, br d, J=5.4 Hz), 8.67 (1H, d, J=5.4 Hz), 9.10 (1H, s)

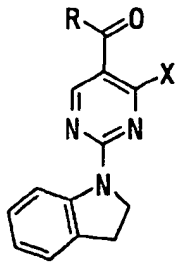
[Table 101]

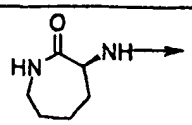
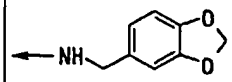
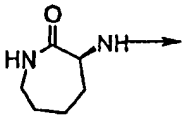
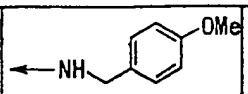


Example No.	R	X	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
66-20			54	1.30-1.70 (5H, m), 1.73-2.23 (4H, m), 2.71 (1H, d, J=16.8 Hz), 3.22-3.50 (3H, m), 3.80 (3H, s), 4.75 (1H,

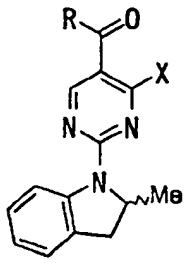
				dd, J=5.8, 9.4 Hz), 4.90-5.08 (1H, m), 5.65 (2H, s), 5.95 (1H, br t, J=7.0 Hz), 6.88-7.05 (3H, m), 7.18-7.30 (2H, m), 7.50 (2H, d, J=8.6 Hz), 8.32 (1H, d, J=7.6 Hz), 8.77 (1H, d, J=5.6 Hz), 9.07 (1H, s)
66-21			55	1.30-1.60 (5H, m), 1.70-2.24 (4H, m), 2.71 (1H, d, J=15.8 Hz), 3.22-3.50 (3H, m), 3.80 (3H, s), 4.74 (1H, dd, J=6.4, 10.0 Hz), 5.03 (1H, quintet, J=8.0 Hz), 5.66 (2H, s), 5.90-6.02 (1H br), 6.84-7.04 (3H, m), 7.20-7.30 (2H, m), 7.50 (2H, d, J=8.4 Hz), 8.32 (1H, d, J=7.6 Hz), 8.77 (1H, d, J=6.6 Hz), 9.08 (1H, s)

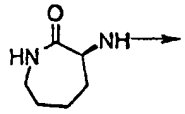
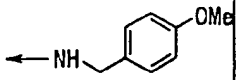
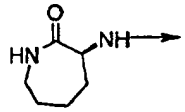
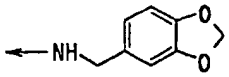
[Table 102]



Example No.	R	X	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
66-22			32	501 $(M+H)^+$
66-23			98	487 $(M+H)^+$

[Table 103]

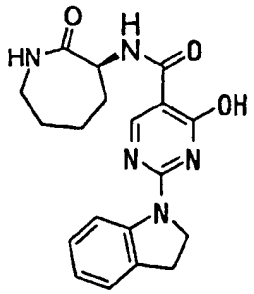


Example No.	R	X	yield (%)	MASS spectrum (APCIMS, m/z) ^{1}H-NMR(δ ppm, $CDCl_3$)
66-24			92	501 $(M+H)^+$
66-25			32	515 $(M+H)^+$

Example 67

2-(2,3-dihydro-1H-indol-1-yl)-4-hydroxy-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

[0360]



[0361] 2-(2,3-Dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide (98 mg, 0.2 mmol) was dissolved in trifluoroacetic acid (0.5 mL) and the mixture was stirred at room temperature for 15 min. Water was added to the reaction mixture, and the precipitated crystals were collected by filtration, washed several times with water and ether, and dried with heating under vacuum to give the title compound (70 mg, 91%). ^{1}H-NMR (δ ppm, $CDCl_3$): 1.50-2.30 (4H, m), 3.20-3.40 (4H, m), 3.50-3.85 (2H, m), 4.32 (2H, t, J=8.0 Hz), 4.72-4.83 (1H, m), 6.63-6.74 (1H, m), 7.00-7.10 (1H, m), 7.17-7.28 (2H, m), 8.42 (1H, d, J=7.8 Hz), 8.83 (1H, s), 9.74 (1H, br s)

Example 68-1

4-({[2-(2,3-dihydro-1H-indol-1-yl)-5-({[(3S)-2-oxoazepanyl]amino}carbonyl)-4-pyrimidinyl]oxy}methyl)-phenylacetate

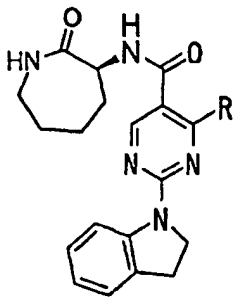
[0362] To a solution of 2-(2,3-dihydro-1H-indol-1-yl)-4-hydroxy-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide (37 mg, 0.1 mmol) in N,N-dimethylformamide (1 mL) were added potassium carbonate (28 mg, 0.2 mmol), sodium iodide (14 mg, 0.1 mmol) and 4-chloromethylphenylacetate (0.023 mL, 0.15 mmol) and the mixture was stirred at 60°C for 2 h. Water was added to the reaction mixture, and the precipitated crystals were collected by filtration, washed several times with water and ether, and dried with heating under vacuum to give the title compound (34 mg, 72%).

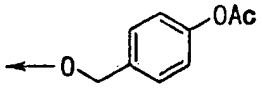
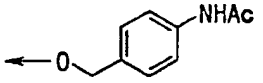
[0363] In the same manner as in Example 68-1, a compound of Example 68-2 was synthesized.

Example 68-2: 4-{[4-(acetylamino)benzyl]oxy}-2-(2,3-dihydro-1H-indol-1-yl)-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide

[0364] Respective structural formulas and NMR data are shown in the following Table.

[Table 104]

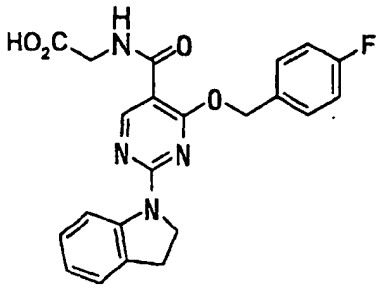


Example No.	R	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
68-1		72	1.30-1.70 (6H, m), 1.70-2.35 (4H, m), 3.14-3.40 (3H, m), 4.29 (2H, t, J=9.2 Hz), 4.70-4.81 (1H, m), 5.71 (2H, s), 5.90 (1H, br t, J=7.6 Hz), 6.95-7.44 (5H, m), 7.60 (2H, d, J=8.4 Hz), 8.28-8.40 (1H, br), 8.70 (1H, d, J=6.2 Hz), 9.10 (1H, s)
68-2		62	1.30-1.70 (3H, m), 1.70-2.38 (7H, m), 3.15-3.40 (3H, m), 4.30 (2H, t, J=8.0 Hz), 4.70-4.85 (1H, m), 5.68 (2H, s), 5.83-6.00 (1H, m), 6.60-6.80 (1H, br), 6.85-7.32 (5H, m), 7.52 (2H, s), 8.20-8.40 (1H, br), 8.78 (1H, d, J=7.0 Hz), 9.09 (1H, s)

Example 69-1

2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl}carbonyl)amino]acetic acid

[0365]



[0366] t-Butyl 2-[({2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-fluorobenzyl)oxy]-5-pyrimidinyl)carbonyl)amino]acetate (210 mg, 0.4 mmol) was dissolved in trifluoroacetic acid -dichloromethane (4:1, 2 mL) and the mixture was stirred at room temperature for 15 min. The reaction mixture was concentrated under reduced pressure and the precipitated crystals were recrystallized from ethyl acetate to give the title compound (140 mg, 70%).
^{1}H-NMR (δ ppm, DMSO-d_6): 3.18 (3H, t, J=8.6 Hz), 3.99 (2H, d, J=5.4 Hz), 4.24 (3H, t, J=8.8 Hz), 5.68 (1H, s), 6.98 (1H, t, J=7.4 Hz), 7.14-7.30 (4H, m), 7.62 (2H, dd, J=5.6 Hz), 8.15-8.30 (2H, m), 8.55 (1H, s)

Example 70

2-(2,3-dihydro-1H-indol-1-yl)-N-[(S)-2-oxoazepanyl]-4-[(RS)-1-phenylethoxy]-5-pyrimidinecarboxamide

Example 71

2-(2,3-dihydro-1H-indol-1-yl)-4-[(RS)-1-phenylethoxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

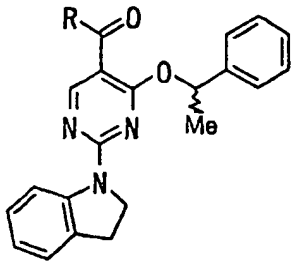
Example 72

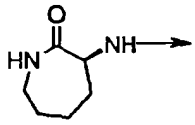
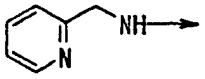
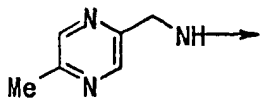
2-(2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-4-[(RS)-1-phenylethoxy]-5-pyrimidinecarboxamide

[0367] In the same manner as in Example 1-1 using ethyl 2-(2,3-dihydro-1H-indol-1-yl)-4-[(RS)-1-phenylethoxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 70 to 72 were synthesized.

[0368] Respective structural formulas and NMR data are shown in the following Table.

[Table 105]



Example No.	R	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
70		53	1.32-2.19 (9H, m), 2.20-2.38 (1H, m), 3.05-3.40 (4H, m), 4.00-4.30 (2H, m), 4.78 (1H, dd, J=5.8, 9.4 Hz), 6.19-6.31 (1H, m), 6.43 (1H, br t, J=6.8 Hz), 6.96 (1H, t, J=7.4 Hz), 7.10-7.53 (6H, m), 8.00-8.40 (1H, br), 9.00-9.20 (2H, m)
71		61	1.87 (3H, d, J=6.6 Hz), 3.17 (2H, t, J=8.8 Hz), 4.00-4.32 (3H, m), 4.84 (2H, d, J=4.4 Hz), 6.46 (1H, q, J=6.2 Hz), 6.97 (1H, t, J=6.6 Hz), 7.12-7.40 (6H, m), 7.49 (2H, dd, J=1.8, 8.0 Hz), 7.70 (1H, dt, J=1.4, 7.6 Hz), 8.00-8.40 (1H, br), 8.56 (1H, d, J=4.4 Hz), 9.02 (1H, s), 9.15 (1H, s)
72		72	1.84 (3H, d, J=6.6 Hz), 2.58 (3H, s), 3.17 (2H, t, J=8.8 Hz), 4.00-4.30 (3H, m), 4.83 (2H, d, J=4.8 Hz), 6.45 (1H, q, J=6.6 Hz), 6.97 (1H, t, J=8.4 Hz), 7.13-7.50 (6H, m), 8.00-8.35 (1H, br), 8.38 (1H, s), 8.55 (1H, s), 8.75 (1H, t, J=5.0 Hz), 9.13 (1H, s)

Example 73

2-[(R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(S)-2-oxoazepanyl]-4-[(RS)-1-phenylethoxy]-5-pyrimidinecarboxamide

Example 74

2-[(R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-4-[(RS)-1-phenylethoxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide

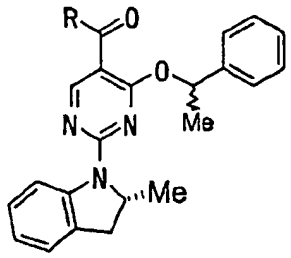
Example 75

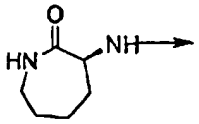
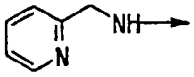
2-[(R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(5-methyl-2-pyrazinyl)methyl]-4-[(RS)-1-phenylethoxy]-5-pyrimidinecarboxamide

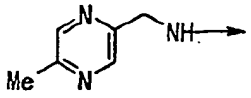
[0369] In the same manner as in Example 1-1 using ethyl 2-[(R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-4-[(RS)-1-phenylethoxy]-5-pyrimidinecarboxylate as a starting material, compounds of Examples 73 to 75 were synthesized.

[0370] Respective structural formulas and NMR data are shown in the following Table.

[Table 106]



Example No.	R	yield (%)	^{1}H-NMR(δ ppm, $CDCl_3$)
73		36	1.20-2.15 (12H, m), 2.20-2.37 (1H, m), 2.65 (1H, d, J=15.4 Hz), 3.10-3.44 (3H, m), 4.70-5.00 (2H, m), 6.30-6.51 (1H, m), 6.52-6.70 (1H, m), 6.98 (1H, t, J=7.2 Hz), 7.08-7.59 (7H, m), 8.00-8.33 (1H, m), 9.00-9.20 (1H, m)
74		46	1.30-1.50 (3H, m), 1.85 (3H, d, J=6.0 Hz), 2.66 (1H, d, J=15.8 Hz), 3.27-3.45 (1H, m), 4.70-5.05 (4H, m), 6.35-6.52 (1H, m), 6.98 (1H, t, J=6.8 Hz), 7.04-7.60 (8H, m), 7.69 (1H, t, J=7.6 Hz), 8.00-8.38 (1H, m), 8.55 (1H, d, J=4.0 Hz). 9.01 (1H, s), 9.14 (1H, s)

75		37	1.20-1.40 (3H, m), 1.83 (3H, t, J=6.2 Hz), 2.50-2.71 (4H, m), 3.28-3.48 (1H, m), 4.70-5.03 (3H, m), 6.32-6.50 (1H, m), 6.99 (1H, t, J=7.0 Hz), 7.01-7.50 (6H, m), 8.00-8.40 (3H, m), 8.55 (1H, s), 8.73 (1H, s), 9.13 (1H, s)

Formulation Example 1

[0371]

(1) Example compound 66-14	10	mg
(2) lactose	60	mg
(3) cornstarch	35	mg
(4) gelatin	3	mg
(5) magnesium stearate	2	mg

[0372] A mixture of Example compound 66-14 (10 mg), lactose (60 mg) and cornstarch (35 mg) was granulated using a 10% aqueous gelatin solution (0.03 ml, 3 mg of gelatin) by passing through a 1 mm mesh sieve, which granules were dried at 40°C and passed through the sieve again. The thus-obtained granules were mixed with magnesium stearate (2 mg) and compressed. The obtained core tablet was coated with a sugar coating containing an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets were polished with beeswax to give coated tablets.

Example 2

[0373]

(1) Example compound 66-14	10	mg
(2) lactose	70	mg
(3) cornstarch	50	mg
(4) soluble starch	7	mg
(5) magnesium stearate	3	mg

[0374] Example compound 66-14 (10 mg) and magnesium stearate (3 mg) were granulated using an aqueous soluble starch solution (0.07 ml, 7 mg of soluble starch), dried and mixed with lactose (70 mg) and cornstarch (50 mg). The mixture was compressed to give tablets.

Example 3

[0375]

(1) Example compound 66-14	5 mg
(2) common salt	20 mg
(3) distilled water	to the total amount of 2 ml

[0376] Example compound 66-14 (5 mg) and common salt (20 mg) were dissolved in distilled water. Water was added to make the total amount 2 ml. The solution was filtered and aseptically filled in 2 ml ampoules. The ampoules were sterilized and sealed to give a solution for injection.

Experimental Example 1

(1) Cloning of gene encoding PDE V derived from human lung

[0377] cDNA was cloned using a gene trapper positive selection system (Gibco BRL). The selected *Escherichia coli* was cultured and DNA was extracted, reacted using Thermo Sequenase Core Sequencing Kit (Amersham), and the nucleotide sequence of cDNA fragment was determined by SQ-3000 DNA sequencer (Hitachi). The obtained clone had a sequence consisting of 3036 bases containing a sequence consisting of 2499 bases depicted in SEQ ID No.:2. This cDNA fragment coded for novel PDE V consisting of 833 amino acids depicted in SEQ ID No.:1. The homology at the amino acid level with known bovine-derived PDE V (Linda M. McAllister et al., J. Biol. Chem. 268(30), 22863 (1993), NCBI GenBank Accession No. L16545) was 92%. A plasmid pPDE50 containing DNA encoding PDE V derived from human lung of the present invention was introduced into *Escherichia coli* (Escherichia coli) DH10B to give a transformant: *Escherichia coli* (Escherichia coli) DH10B/pPDE50.

(2) Construction of *Escherichia coli* expression vector

[0378] The cDNA encoding PDE V derived from human lung obtained in the above-mentioned (1) was cleaved with EcoRI and XhoI, and ligated with pGEX4T-2 (Pharmacia Biotech) treated in the same manner. Using a ligation solution, *Escherichia coli* BL21 (Funakoshi) was transformed to give *Escherichia coli* (Escherichia coli) BL21/pPDE51 that expresses PDE V derived from human lung of the present invention.

[0379] This transformant: *Escherichia coli* BL21/pPDE51 has been deposited at the National Institute of Bioscience and Human-Technology (NIBH) since July 13, 1998 under deposit No. FERM BP-6417 and at the Institute for Fermentation, Osaka under deposit No. IFO 16185 since June 18, 1998.

(3) Expression and purification of recombinant type PDE V derived from human lung in *Escherichia coli*

[0380] Using *Escherichia coli* BL21/pPDE51 obtained in the above-mentioned (2), recombinant type PDE V derived from human lung of the present invention was obtained. The expression and purification by *Escherichia coli* were done in accordance with the protocol attached to GST Gene Fusion System (Pharmacia Biotech). As a result, 12.5 mg of the objective ca. 100 kDa recombinant type PDE V derived from human lung was obtained from 1 L of *Escherichia coli* culture.

(4) Detection of PDE activity of PDE V derived from human lung

[0381] The PDE activity of PDE V derived from human lung was detected using Phosphodiesterase [^{3}H]cGMP SPA enzyme assay kit (Amersham). As a result, PDE activity was acknowledged in the enzyme solution obtained in the above-mentioned (2). BL21 was transformed with pGEX4T-2 and used as a control. This did not show PDE activity.

(5) Designing inhibitor search system

[0382] Into a 96 well plate (OPTI plate, Packard) was added a buffer [10 μl, 0.5M Tris-HCl (pH 7.5), 83 mM $MgCl_2$ and 17 mM EGTA], the recombinant type PDE V derived from human lung (10 μl, 0.025 mg/ml) obtained in the above-mentioned (3), ultrapure water (65 μl), inhibitor sample (5 μl) and [^{3}H]cGMP (10 μl), and the mixture was allowed to react at 30°C for 30 min. After the completion of the reaction, SPA beads solution [50 μl, 18 mg/ml Yttrium silicate beads, 18 mM $ZnSO_4$] was added and the mixture was stood at room temperature for about 20 min, after which applied to measurement with a scintillation counter (Topcount, Packard). In contrast to the radioactivity (1780 cpm) without addition, the radioactivity of 10367 cpm was observed when the recombinant type PDE V derived from human lung was added. Addition of various concentrations of sildenafil (Drugs of Future 22(2), 1997), which is an inhibitor of PDE V, to this reaction resulted in the inhibition of PDE activity. About 2 nM of sildenafil inhibited the enzyme reaction by 50%. Based on such results, it was confirmed that search of PDE inhibitor is possible using this assay system.

(6) Practicing inhibitor search

[0383] Using the method designed in the above-mentioned (5), the representative compound of the present invention was measured for recombinant type human lung derived PDE inhibitory activity (IC_{50} value). The results are shown in Table 107.

[Table 107]

Example	PDE inhibitory activity (IC_{50}:nM)
31-6	1.47
33-3	0.582
66-6	0.304

Industrial Applicability

[0384] The compound (I), a salt thereof and a prodrug thereof of the present invention have a potent and selective cGMP-PDE, particularly cGMP-PDE V, inhibitory activity, and can be used as an agent for the prophylaxis or treatment of diseases caused by promoted metabolism of cGMP (e.g., angina pectoris, heart failure, cardiac infarction, hypertension, pulmonary hypertension, arteriosclerosis, allergic diseases, asthma, renal diseases, cerebral function disorders, immunodeficiency, ophthalmic diseases, or disorders of male or female genital function and the like).

SEQUENCE LISTING

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<120> Pyrimidine-5-Carboxamide Compounds, Their Production And Use

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Lys Ile Thr Asp Phe Ser Phe Ser Asp Phe Glu Leu Ser Asp Leu Glu
515 520 525

Thr Ala Leu Cys Thr Ile Arg Met Phe Thr Asp Leu Asn Leu Val Gln
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Asn Phe Gln Met Lys His Glu Val Leu Cys Arg Trp Ile Leu Ser Val
545 550 555 560

Lys Lys Asn Tyr Arg Lys Asn Val Ala Tyr His Asn Trp Arg His Ala
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Phe Asn Thr Ala Gln Cys Met Phe Ala Ala Leu Lys Ala Gly Lys Ile
580 585 590

Gln Asn Lys Leu Thr Asp Leu Glu Ile Leu Ala Leu Leu Ile Ala Ala

595 600 605

Leu Ser His Asp Leu Asp His Arg Gly Val Asn Asn Ser Tyr Ile Gln

610 615 620

Arg Ser Glu His Pro Leu Ala Gln Leu Tyr Cys His Ser Ile Met Glu

625 630 635 640

His His His Phe Asp Gln Cys Leu Met Ile Leu Asn Ser Pro Gly Asn

645 650 655

Gln Ile Leu Ser Gly Leu Ser Ile Glu Glu Tyr Lys Thr Thr Leu Lys

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Ile Ile Lys Gln Ala Ile Leu Ala Thr Asp Leu Ala Leu Tyr Ile Lys

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690 695 700

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705 710 715 720

Cys Asp Leu Ser Ala Ile Thr Lys Pro Trp Pro Ile Gln Gln Arg Ile

725 730 735

Ala Glu Leu Val Ala Thr Glu Phe Phe Asp Gln Gly Asp Arg Glu Arg

740 745 750

Lys Glu Leu Asn Ile Glu Pro Thr Asp Leu Met Asn Arg Glu Lys Lys

755 760 765

Asn Lys Ile Pro Ser Met Gln Val Gly Phe Ile Asp Ala Ile Cys Leu

770 775 780

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CTAGATGGCT GCAGAAAGAA CAGGCAGAAA TGGCAGGCCC TTGCAGAACA GCAGGAGAAG 2460

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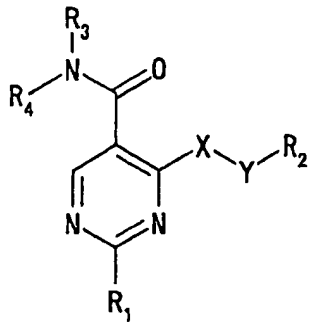
Claims

1. A compound of the formula



wherein

R_1 is a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 nitrogen atom(s), which heterocycle is attached by a secondary nitrogen atom constituting the heterocycle;

X is an oxygen atom, a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom (s) or a sulfur atom optionally oxidized with 1 or 2 oxygen,

Y is a bond or a C_{1-5} alkylene group,

R_2 is (1) a hydrogen atom, (2) a hydroxy group, (3) a C_{1-5} alkoxy group, (4) a C_{1-5} alkylthio group, (5) a carbocycle having 3 to 15 carbon atoms or (6) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s),

provided that when Y is a bond, R_2 is a carbocycle having 3 to 15 carbon atoms or a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and;

one of R_3 and R_4 is a hydrogen atom or a group of the formula: -Z-R_5 (Z is a bond or C_{1-10} alkylene group optionally having substituent(s) and R_5 is (1) a hydrogen atom, (2) a hydroxy group, (3) a C_{1-5} alkoxy group, (4) a nitrile group, (5) a C_{1-5} alkoxy-carbonyl group, (6) a carboxyl group, (7) a carbamoyl group, (8) a (mono or di-C_{1-5} alkyl)carbamoyl group, (9) an amino group, (10) a (di or mono-C_{1-5} alkyl)amino group, (11) a (C_{1-5} alkoxy-carbonyl)amino group, (12) a C_{1-5} alkylthio group, (13) a carbocycle having 3 to 15 carbon atoms or (14) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s));

the other R_3 and R_4 is a group of the formula: -Z-R_5 (Z and R_5 are as defined above); and may form, together with the adjacent nitrogen atom, a heterocycle having a skeleton consisting of 3 to 15 atoms, which heterocycle is attached by a secondary nitrogen atom constituting the heterocycle, wherein the above-mentioned heterocycle and a carbocycle having 3 to 15 carbon atoms are each optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl) amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl,

or a salt thereof.

2. The compound of claim 1, wherein, when Z is a C_{2-10} alkylene group optionally having substituent(s), R_5 is a hydrogen atom, a hydroxy group, a C_{1-5} alkoxy group, a nitrile group, a C_{1-5} alkoxy-carbonyl, a carboxyl group, a carbamoyl group, a (mono or di-C_{1-5} alkyl)carbamoyl group, an amino group, a (di or mono-C_{1-5} alkyl)amino group, a (C_{1-5} alkoxy-carbonyl)amino group, a C_{1-5} alkylthio group, a carbocycle having 3 to 15 carbon atoms, or a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and, when Z is a methylene group optionally having substituents, R_5 is a nitrile group, a C_{1-5} alkoxy-carbonyl group, a carboxyl group, a carbamoyl group, a (mono or di-C_{1-5} alkyl)carbamoyl group, a carbocycle having 3 to 15 carbon atoms, or a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s).

3. The compound of claim 1, wherein X is a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom(s) or a sulfur atom optionally oxidized with 1 or 2 oxygen.

4. The compound of claim 1, wherein Y is a C_{2-5} alkylene group.

5. The compound of claim 1, wherein Y is a C_{1-5} alkylene group, R_2 is a hydroxy group, a C_{1-5} alkoxy group or a C_{1-5} alkylthio group.

6. The compound of claim 1, wherein R_5 is (1) a non-aromatic carbocycle having 3 to 15 carbon atoms or (2) a non-aromatic heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s).

7. The compound of claim 1, wherein Z is a C_{2-10} alkylene group optionally having substituent(s), and R_5 is a hydroxy group, a nitrile group, a C_{1-5} alkoxy-carbonyl, a carboxyl group, a carbamoyl group, a (mono or di-C_{1-5} alkyl) carbamoyl group, a (C_{1-5} alkoxy-carbonyl)amino group or a C_{1-5} alkylthio group.

8. The compound of claim 1, wherein Z is a methylene group optionally having substituent(s), and R_5 is a nitrile group, a C_{1-5} alkoxy-carbonyl group, a carboxyl group, a carbamoyl group or a (mono or di-C_{1-5} alkyl)carbamoyl group.

9. The compound of claim 1, wherein the substituent(s) of the heterocycle and the carbocycle having 3 to 15 carbon atoms is selected from the group consisting of C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-3} alkylenedioxy, hydroxy, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl)(C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl.

10. The compound of claim 1, wherein R_1 is a heterocycle having a skeleton consisting of 5 to 12 atoms including 1 or 2 nitrogen atom(s) and optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl)(C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl) sulfamoyl.

11. The compound of claim 1, wherein R_1 is a heterocycle having a skeleton consisting of 8 to 12 atoms including a nitrogen atom and optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl) amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl.

12. The compound of claim 1, wherein R_1 is 1-indolinyl optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl) amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl.

13. The compound of claim 1, wherein R_2 is a carbocycle having 5 to 7 carbon atoms or a heterocycle having a skeleton consisting of 5 to 7 atoms including 1 or 2 heteroatom(s), which heterocycle is optionally substituted by substituent (s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl) amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl) sulfamoyl.

14. The compound of claim 1, wherein R_2 is phenyl optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl) amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl.

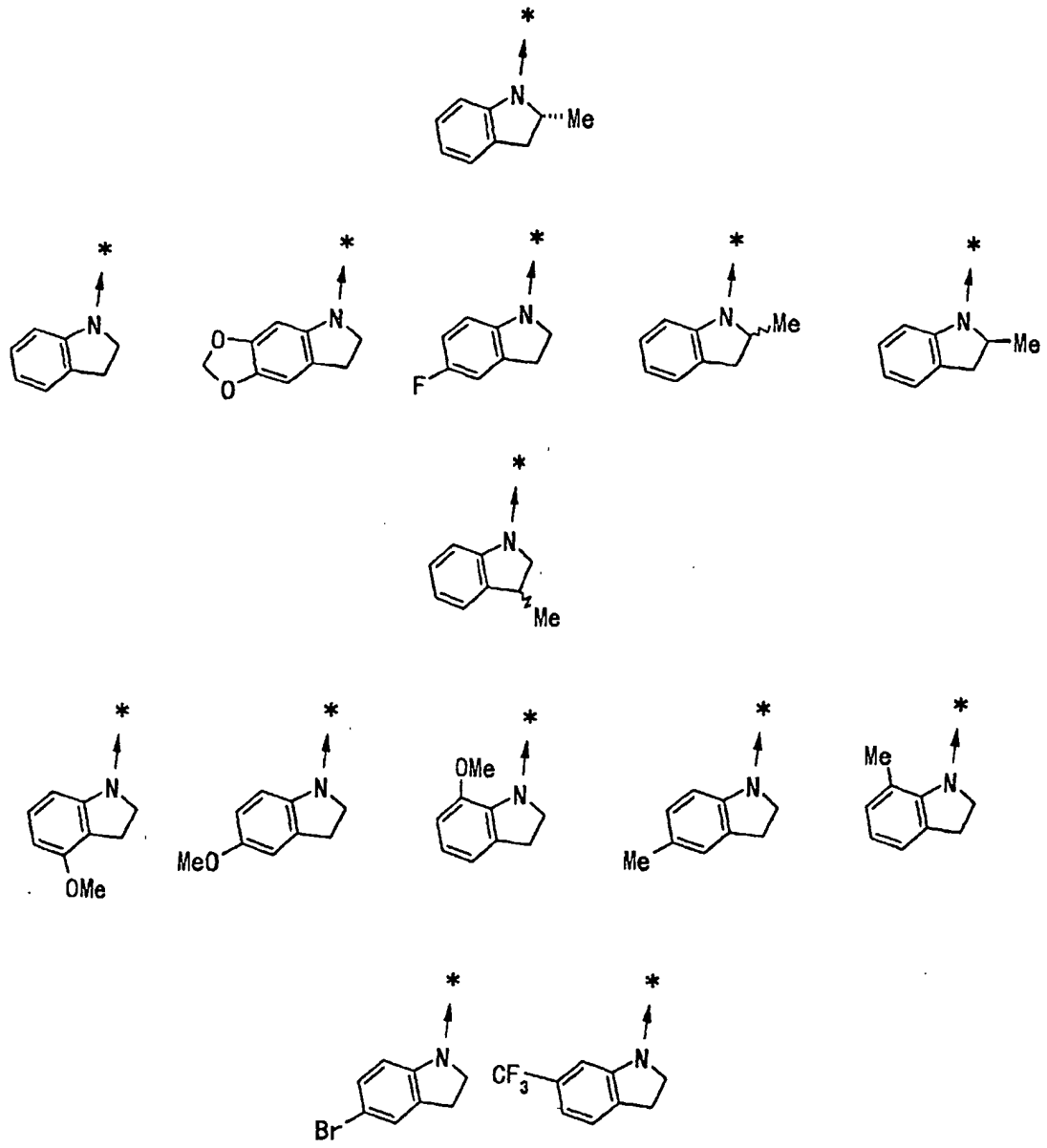
15. The compound of claim 1, wherein X is an oxygen atom or NH, and Y is a C_{1-3} alkylene group.

16. The compound of claim 1, wherein X is an oxygen atom, and Y is a methylene group.

17. The compound of claim 1, wherein R_3 is a hydrogen atom and R_4 is a group of the formula: -Z-R_5.

18. The compound of claim 17, wherein Z is a bond or a C_{1-4} alkylene group, R_5 is a carbocycle having 5 to 8 carbon atoms or a heterocycle having a skeleton consisting of 5 to 11 atoms having 1 to 5 heteroatom(s), which heterocycle is optionally substituted by substituent(s) selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{7-16} aralkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{1-8} alkoxy, C_{1-3} alkylenedioxy, hydroxy, halogen atom, amino, (di or mono-C_{1-5} alkyl)amino, (C_{1-5} alkoxy-carbonyl)amino, (C_{1-5} acyl)amino, (C_{1-5} acyl) (C_{1-5} alkyl)amino, C_{1-5} alkylthio, nitrile, nitro, C_{1-5} alkoxy-carbonyl, carboxyl, C_{1-5} alkyl-carbonyloxy, oxo, thioxo, C_{1-6} acyl group, sulfamoyl and (di or mono-C_{1-5} alkyl)sulfamoyl.

19. The compound of claim 1, wherein R_1 is a group selected from



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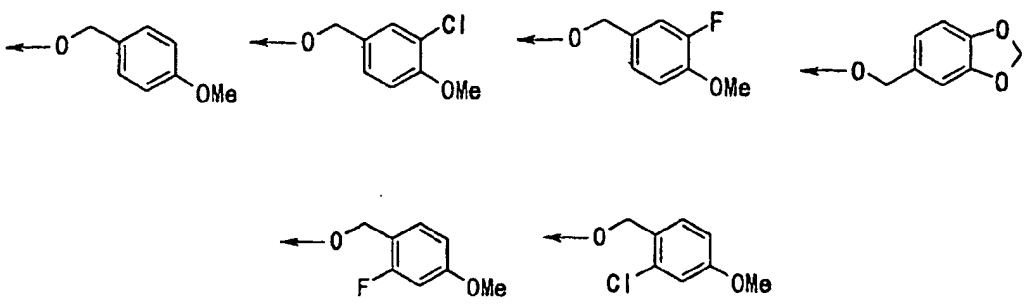
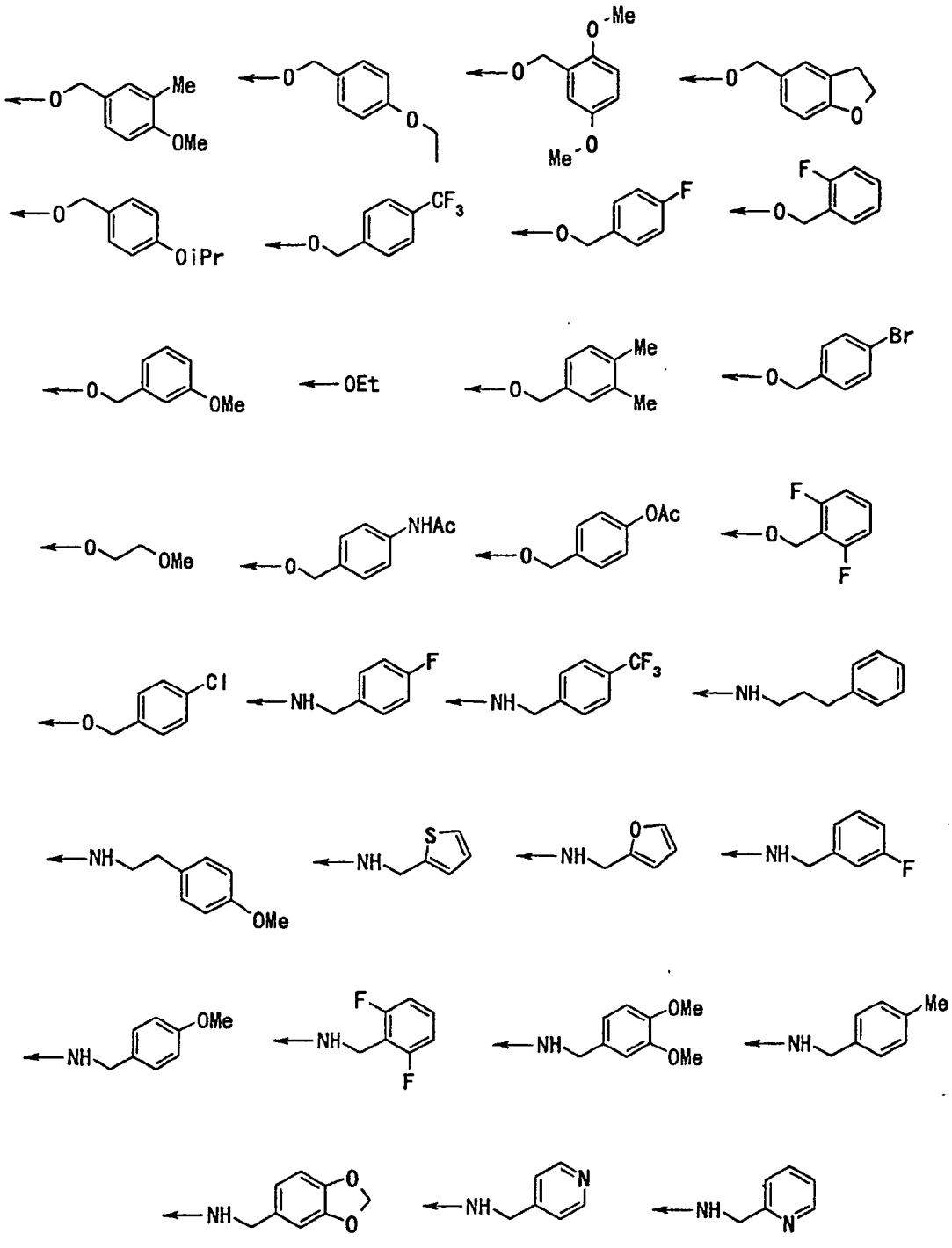
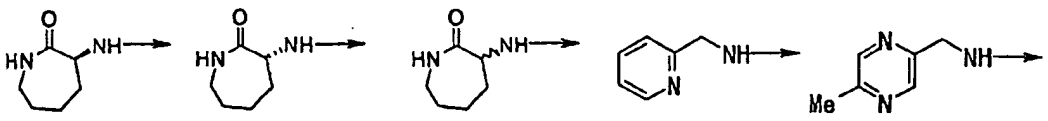
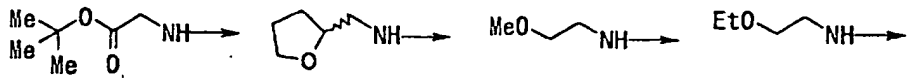
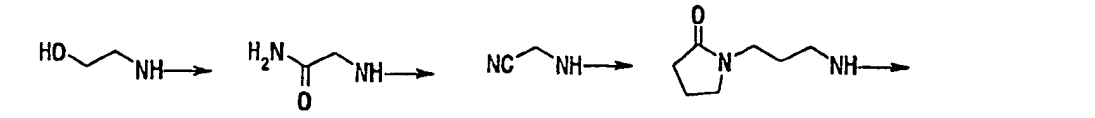


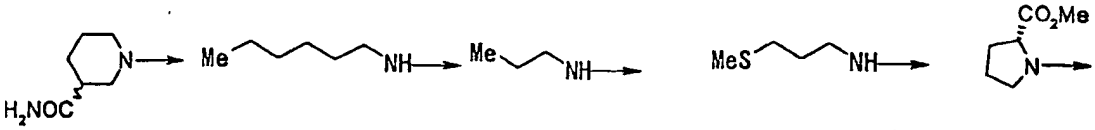


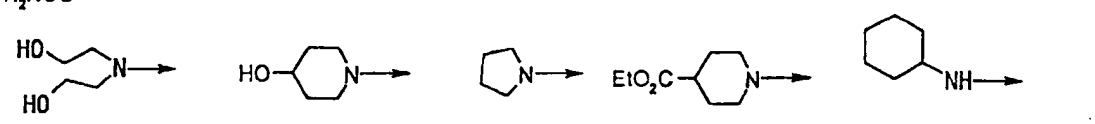
, and $-NR_3R_4$ is a group selected from

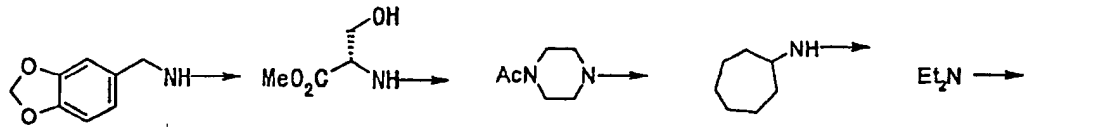


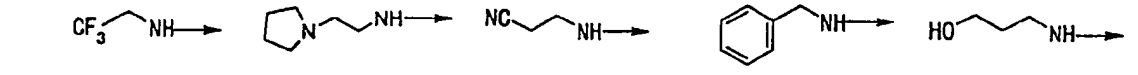


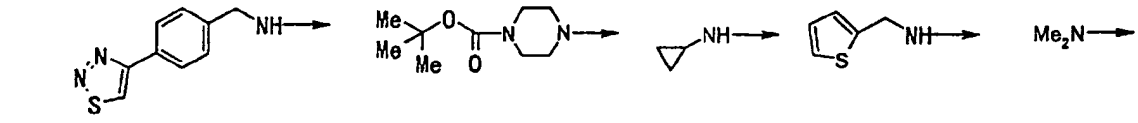


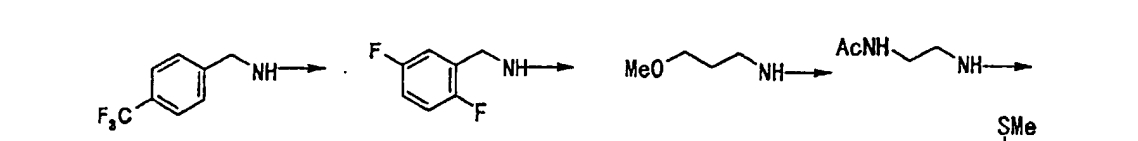


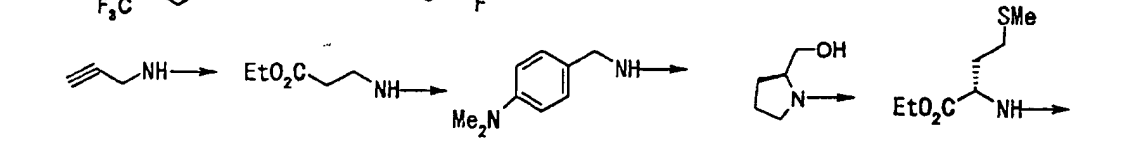


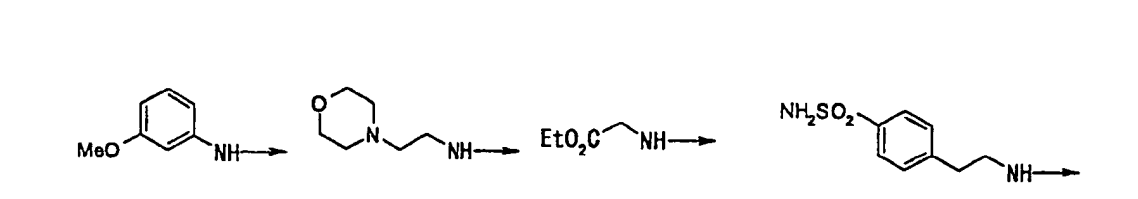


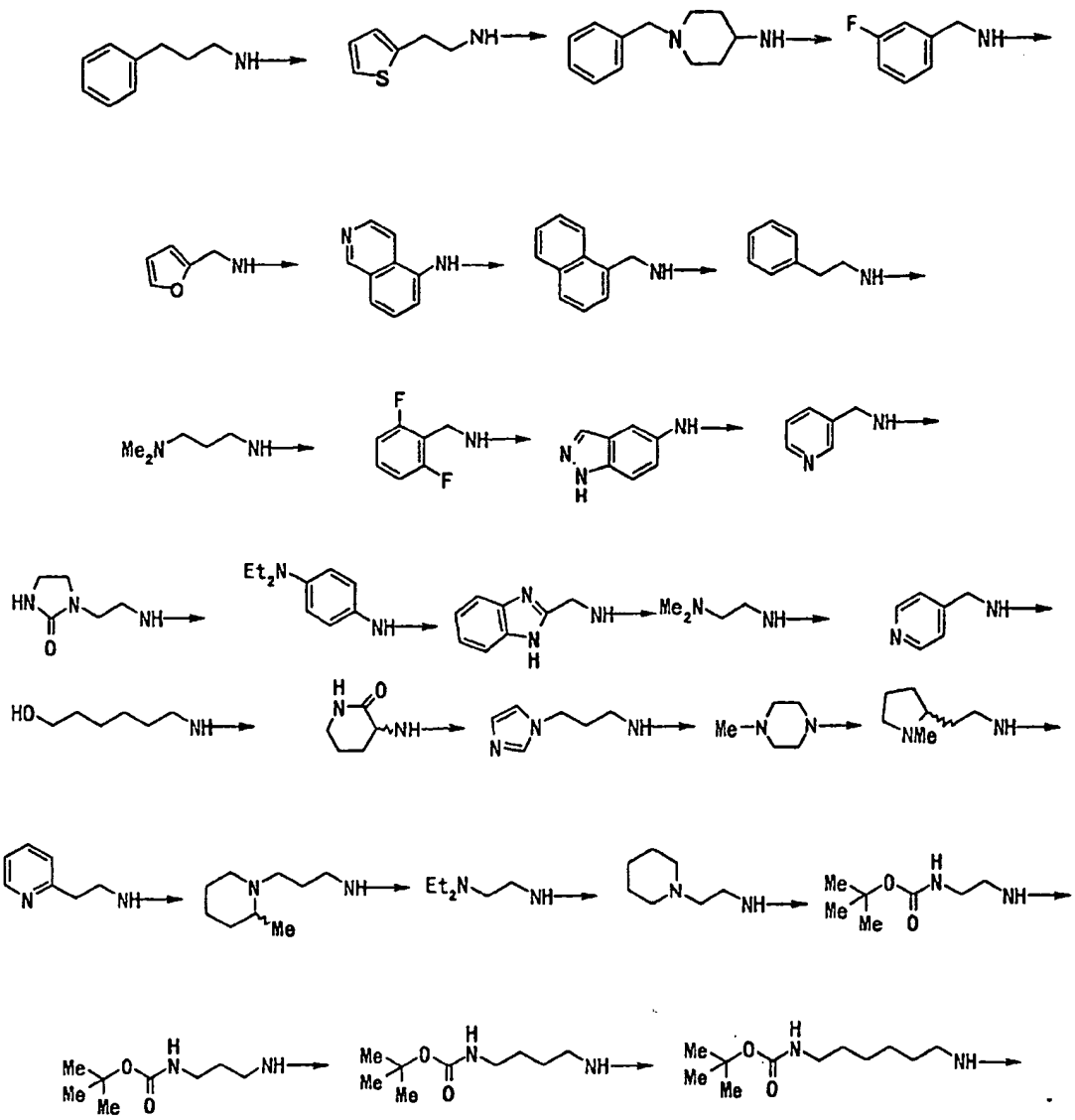




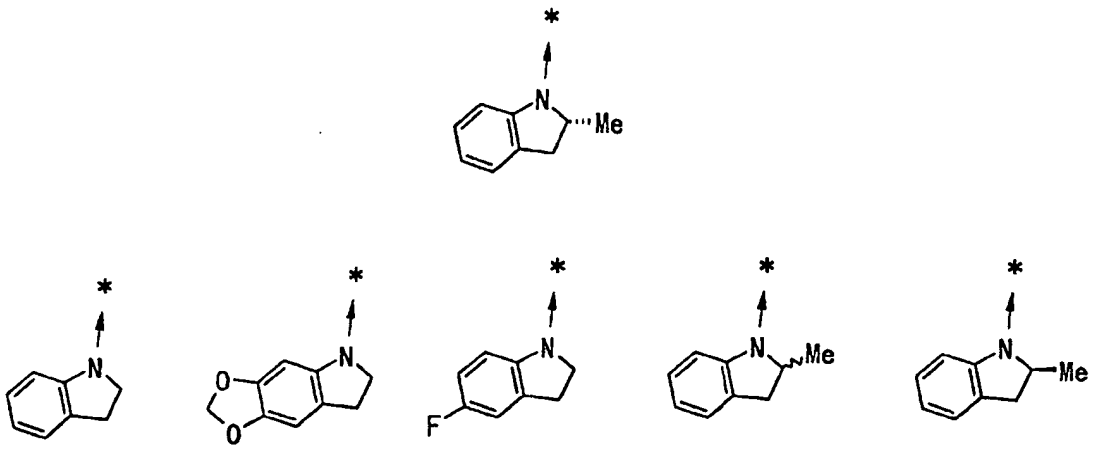


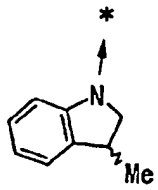




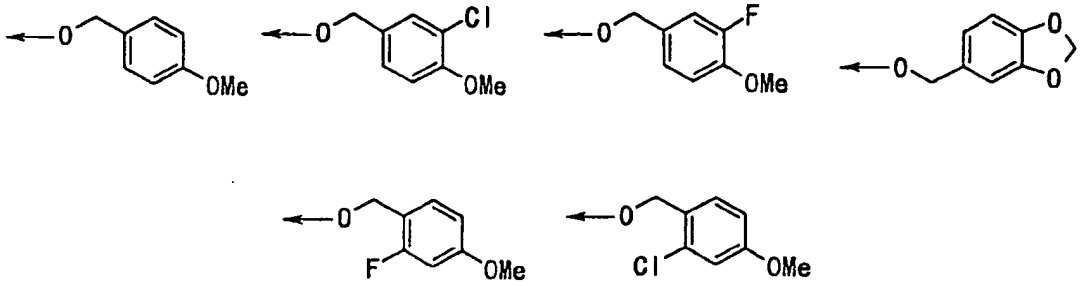


20. The compound of claim 1, wherein R_1 is a group selected from

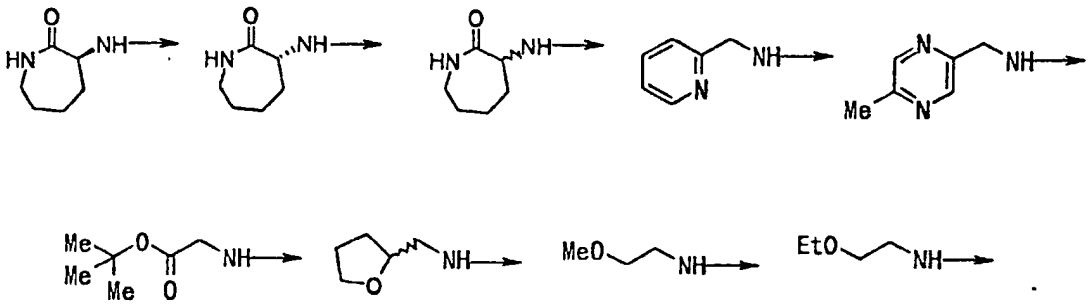




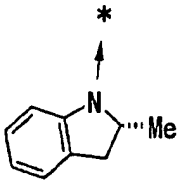
, -X-Y-R_2 is a group selected from



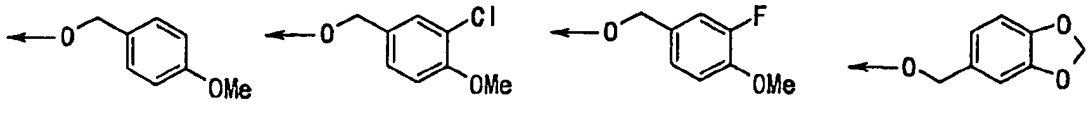
, and -NR_3R_4 is a group selected from



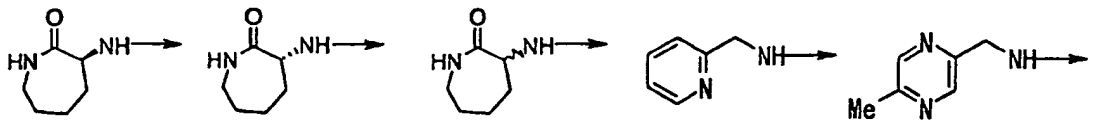
21. The compound of claim 1, wherein R_1 is a group selected from the group consisting of



, -X-Y-R_2 is a group selected from the group consisting of



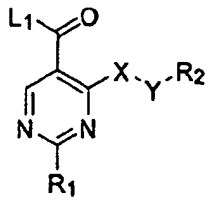
, and -NR_3R_4 is a group selected from the group consisting of



22. (i) (RS)-2-(2,3-Dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide (ii) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide, (iii) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide, (iv) (RS)-4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide, (v) 4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide, (vi) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide, (vii) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide, (viii) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide, (ix) 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-pyridinylmethyl)-5-pyrimidinecarboxamide, (x) 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide, (xi) 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-pyrazinyl)methyl]-5-pyrimidinecarboxamide, (xii) (rac)-4-[(4-methoxybenzyl)oxy]-2-(2-methyl-2,3-dihydro-1H-indol-1-yl)-N-(2-oxo-3-azepanyl)-5-pyrimidinecarboxamide, (xiii) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xiv) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xv) 4-(1,3-benzodioxol-5-ylmethoxy)-2-(2,3-dihydro-1H-indol-1-yl)-4-[(4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xvi) 2-(2,3-dihydro-1H-indol-1-yl)-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xvii) 4-[(3-chloro-4-methoxybenzyl)oxy]-2-(2,3-dihydro-1H-indol-1-yl)-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xviii) 4-[(4-methoxybenzyl)oxy]-2-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xix) 4-[(4-methoxybenzyl)oxy]-2-[(2RS)-2-methyl-2,3-dihydro-1H-indol-l-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xx) 4-[(4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xxi) 4-[(4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xxii) 2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-4-[(3-fluoro-4-methoxybenzyl)oxy]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xxiii) 4-[(3-chloro-4-methoxybenzyl)oxy]-2-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide, (xxiv) 4-[(4-methoxybenzyl)oxy]-2-[(2S)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3S)-2-oxoazepanyl]-5-pyrimidinecarboxamide or (xxv) 4-[(4-methoxybenzyl)oxy]-2-[(2S)-2-methyl-2,3-dihydro-1H-indol-1-yl]-N-[(3R)-2-oxoazepanyl]-5-pyrimidinecarboxamide.

23. A prodrug of the compound of claim 1.

24. A production method of the compound of claim 1, which comprises reacting a compound of the formula



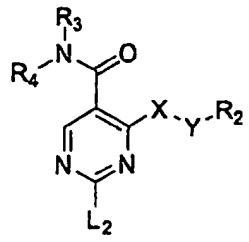
(II)

wherein L_1 is a leaving group and other symbols are as defined in claim 1, or a salt thereof, with an amine compound of the formula

$$R_3R_4NH$$

wherein R_3 and R_4 are as defined in claim 1.

25. A production method of the compound of claim 1, which comprises reacting a compound of the formula



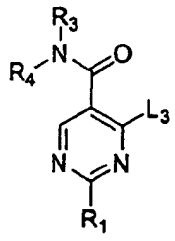
(III)

wherein L_2 is a leaving group and other symbols are as defined in claim 1, or a salt thereof, with a compound of the formula

$$R_1\text{-}H$$

wherein R_1 is as defined in claim 1.

26. A production method of the compound of claim 1, which comprises reacting a compound of the formula



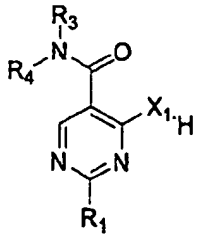
(IV)

wherein L_3 is a leaving group and other symbols are as defined in claim 1, or a salt thereof, with a compound of the formula

$$R_2\text{-}Y\text{-}X_1\text{-}H$$

wherein R_2 and Y are as defined in claim 1 and X_1 is an oxygen atom, a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom(s) or a sulfur atom, and if desired, subjecting the resulting compound to oxidation.

27. A production method of the compound of claim 1, which comprises reacting a compound of the formula



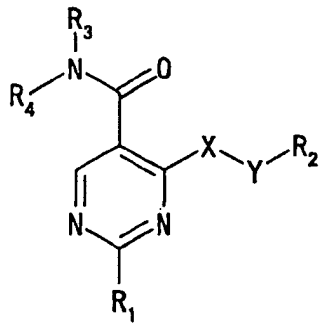
(V)

wherein symbols are as defined in claim 1, X_1 is an oxygen atom, a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom(s) or a sulfur atom, or a salt thereof, with a compound of the formula

R_2-Y-L_4

wherein R_2 and Y are as defined in claim 1 and L_4 is a leaving group, and if desired, subjecting the resulting compound to oxidation.

28. A pharmaceutical composition comprising a compound of the formula



wherein symbols are as defined in claim 1, or a salt thereof or a prodrug thereof.

29. The pharmaceutical composition of claim 28, which is a cyclic guanosine-3',5'-monophosphoric acid phosphodiesterase inhibitor.

30. The pharmaceutical composition of claim 28, which is a composition for the prophylaxis or treatment of angina pectoris, heart failure, cardiac infarction, hypertension, pulmonary hypertension, arteriosclerosis, allergic diseases, asthma, renal diseases, cerebral function disorders, immunodeficiency, ophthalmic diseases or disorders of male or female genital function.

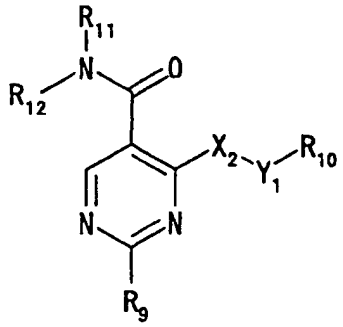
31. A method for inhibiting cyclic guanosine-3',5'-monophosphoric acid phosphodiesterase, which comprises administering an effective amount of the compound of claim 1 or a prodrug thereof to a mammal.

32. A method for the prophylaxis or treatment of angina pectoris, heart failure, cardiac infarction, hypertension, pulmonary hypertension, arteriosclerosis, allergic diseases, asthma, renal diseases, cerebral function disorders, immunodeficiency, ophthalmic diseases or disorders of male or female genital function in a mammal, which comprises administering an effective amount of the compound of claim 1 or a prodrug thereof to the mammal.

33. Use of the compound of claim 1 or a prodrug thereof for the production of a cyclic guanosine-3',5'-monophosphoric acid phosphodiesterase inhibitor.

34. Use of the compound of claim 1 or a prodrug thereof for the production of an agent for the prophylaxis or treatment of angina pectoris, heart failure, cardiac infarction, hypertension, pulmonary hypertension, arteriosclerosis, allergic diseases, asthma, renal diseases, cerebral function disorders, immunodeficiency, ophthalmic diseases or disorders of male or female genital function.

35. A compound of the formula



wherein

R_9 is a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 nitrogen atom(s), and optionally having substituent(s), which heterocycle is attached by a secondary nitrogen atom forming its ring,

X_2 is an oxygen atom, a nitrogen atom optionally substituted by a hydrocarbon group having 1 to 5 carbon atom(s) or a sulfur atom optionally oxidized with 1 or 2 oxygen,

Y_1 is a bond or a C_{1-5} alkylene group,

R_{10} is (1) a hydrogen atom, (2) a hydroxy group, (3) a C_{1-5} alkoxy group, (4) a C_{1-5} alkylthio group, (5) a C_{3-15} carbocycle optionally having substituent(s) or (6) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and optionally having substituent(s), one of R_{11} and R_{12} is a hydrogen atom or a group of the formula: $-Z_1-R_{13}$ (Z_1 is a bond or a C_{1-10} alkylene group optionally having substituent(s)), R_{13} is (1) a hydrogen atom, (2) a hydroxy group, (3) a C_{1-5} alkoxy group, (4) a nitrile group, (5) a C_{1-5} alkoxy-carbonyl group, (6) a carboxyl group, (7) a carbamoyl group, (8) a (mono or di-C_{1-5} alkyl)carbamoyl group, (9) an amino group, (10) a (di or mono-C_{1-5} alkyl)amino group, (11) a (C_{1-5} alkoxy-carbonyl)amino group, (12) a C_{1-5} alkylthio group, (13) a C_{3-15} carbocycle optionally having substituent(s) or (14) a heterocycle having a skeleton consisting of 3 to 15 atoms including 1 to 5 heteroatom(s) and optionally having substituent(s),

the other R_{11} and R_{12} is a group of the formula: $-Z_1-R_{13}$ (Z_1 and R_{13} are as defined above); and may form, together with the adjacent nitrogen atom, a heterocycle having a skeleton consisting of 3 to 15 atoms and optionally having substituent(s) and attached by a secondary nitrogen atom forming its ring], or a salt thereof.

36. A prodrug of the compound of claim 35.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/07048

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D403/04, 401/14, 403/14, 405/14, 409/14, 417/14, 491/056, A61K31/506, 5377, 55, A61P43/00, 9/10, 9/04, 9/12, 37/08, 11/06, 13/12, 25/28, 37/04, 27/02, 15/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D403/04, 401/14, 403/14, 405/14, 409/14, 417/14, 491/056, A61K31/506, 5377, 55, A61P43/00, 9/10, 9/04, 9/12, 37/08, 11/06, 13/12, 25/28, 37/04, 27/02, 15/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS, REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, 99/31073, A1 (YAMANOUCHI PHARMACEUTICAL CO. LTD.), 24 June, 1999 (24.06.99), RN=227449-90-3, 227450-02-4 & AU, 9915071, A & EP, 1054004, A1	1,3,10,11,13, 14,17,23-30, 33-36
X	WO, 99/6046, A1 (KOS PHARMACEUTICALS INC.), 11 February, 1999 (11.02.99), RN=75689-93-9 & AU, 9886800, A & EP, 1003515, A1 & NO, 2000000407, A	35,36
X	DE, 19636487, A (HOECHST A.-G.), 12 March, 1998 (12.03.98) (Family: none)	35,36
X	EP, 816358, A1 (HOECHST A.-G.), 07 January, 1998 (07.01.98), & DE, 19625089, A & US, 5939424, A & CA, 2208630, A & NO, 9702943, A & JP, 10-72463, A	35,36
X	EP, 816359, A1 (HOECHST A.-G.), 07 January, 1998 (07.01.98),	35,36

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 November, 2000 (28.11.00)	12.12.00
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/07048

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& DE, 19625088, A & US, 5773447, A & CA, 2208611, A & NO, 9702942, A & JP, 10-72462, A	
X	EP, 557879, A1 (HOECHST A.-G.), 01 September, 1993 (01.09.93), & CA, 2089954, A & NO, 9300596, A & AU, 9333762, A & HU, 63409, A & ZA, 9301182, A & JP, 6-41120, A & IL, 104791, A & AU, 9510290, A & HU, 70638, A & US, 5571816, A	35,36
X	EP, 557877, A1 (HOECHST A.-G.), 01 September, 1993 (01.09.93), & CA, 2089956, A & NO, 9300595, A & AU, 9333760, A & HU, 63410, A & ZA, 9301183, A & JP, 6-184137, A & IL, 104792, A & AU, 9511365, A & US, 5795899, A & HU, 70503, A	35,36
X	WO, 87/4928, A1 (MITSUI PETROCHEMICAL INDUSTRIES LTD.), 27 August, 1987 (27.08.87), & EP, 257102, A1 & EP, 799617, A2 & US, 4959368, A & CA, 1305142, A & JP, 8-325268, A	1-4,10,11,15, 16,23-28,35,36
X	EP, 188094, A2 (MITSUI PETROCHEMICAL INDUSTRIES LTD.), 23 July, 1986 (23.07.86), & JP, 61-140568, A & US, 4734418, A & CA, 1307786, A & HU, 42479, A	1-4,10,11,15- 18,23-30,33-36
X	EP, 12361, A1 (HOECHST A.-G.), 25 June, 1980 (25.06.80), & DE, 2853220, A & ES, 486536, A & AU, 7953571, A & JP, 55-81863, A & ZA, 7906651, A & US, 4285946, A & CA, 1136623, A & ES, 491224, A & ES, 491225, A	35,36
X	GB, 933159, A (CIBA LTD.), 08 August, 1963 (08.08.63) & US, 3234219, A	35,36
X	GB, 901749, A (CIBA LTD.), 25 July, 1962 (25.07.62)	35,36
X	Chemical Abstracts, Vol.55, column 6489, Par. No. c to column 6491, Par. No. c, RN=102548-49-2	35,36
A	EP, 640599, A1 (ONO PHARMACEUTICAL CO., LTD.), 01 March, 1995 (01.03.95), & US, 5525604, A & JP, 7-89958, A & CA, 2130878, A & CN, 1109055, x	1-30,33-36

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/07048

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 31,32
because they relate to subject matter not required to be searched by this Authority, namely:

The inventions as set forth in claims 31 and 32 pertain to methods for treatment of the human body.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

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